The Psychiatry Letter

The new year reviving old desires

This issue represents the end of the second year of the existence of this newsletter. We would like to thank you who continue to subscribe. The newsletter relies on you to keep going and to spread its influence.

In the past year we have been able to provide Continuing Medical Education (CME) and Continuing Education Units (CEU) to psychiatrists and nurses and psychologists. We hope you continue to benefit from that service.

Last December, in honor of the first year anniversary of the newsletter, we provided a special issue with a Top Ten list of events, studies, and topics in psychiatry in the past year. We continue that tradition with this issue. We also provide another Top Five list of great historical insights in psychiatry.

In reviewing published articles from the past year, it was difficult to identify one study as better than other ones which are excellent or important. Thus we stay with our usual format of a current article of the month instead of seeking to pick a top article for the year. The article chosen this month was released online just recently and provides empirical data on the developmental presentation of depression in children.

If you find PL helpful to you and your patients, please let others know so that more clinicians and patients may benefit.

Happy new year to you and yours,

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley
**Special Article I: Top Ten List of 2016**

Our review of key topics in psychiatry this year

**What's important?**

As with the December 2015 issue, PL continues the tradition of thinking about the last year as the new year approaches, and discussing important topics or debates that have been active in the past year.

As usual PL provides its perspective frankly, though not necessarily here with all the evidence for its conclusions. On the PL website and in PL issues cited, relevant links are provided to articles which provide that further elaboration.

**Number 10: The Snapchat generation**

How should we, or could we, use telemedicine to connect to patients? How does the use of the internet and social media affect our patients? These are key questions that are arising in the last few years and promise to be major questions for the future.

As of now, there are some legal concerns with telemedicine as applied to psychiatry. State boards regulate clinical practice based on where the patient is examined, not based on where the clinician is located. Thus if you do a video interview of a patient in another state, you must have clinical license privileges in the patient's state, not your own. Given this important legal issue, it is questionable whether it is safe to interview and advise or treat patients in other states based on video or telephone interactions.

Legal and governmental bodies are slow to adapt so this process may prove to take a long time, but eventually telepsychiatry will become something more common. Until the legal aspects are worked out, though, it is important to realize that such clinical activity is not protected under current legal standards in relation to out of state interactions.

Regarding the use of the internet by patients, especially adolescents and young adults, it is likely that we are in the midst of a new kind of addiction. Internet addiction is not limited any longer to sexual or pornographic content. Many young persons are addicted to Snapchat or Instagram or other forms of (usually visual) communication. The related matter of cyberbullying has become important as well.

This problem isn't limited to young persons, as the older generations tend to be more connected to Facebook and Twitter, sometimes excessively so. The mental health professions will need to determine how to respond to these developing behaviors. The addiction model is likely to be the most relevant way of understanding the impact of these social media activities.

**Number 9: Should we use mental health apps?**

A related technological matter is the development of apps for mental health content on smartphones. These apps are in their infancy, and it is hard to know which will prove useful and which will not. But there is little doubt that they too will become important in the future as a means of interacting with patients as well as recording their symptoms and management.

Currently, some sleep apps exist which provide sleep study-like measurements of the stages of sleep.
sleep. They may be useful for assessing the effects of insomnia.

Other apps are being developed to treat ADD purportedly, and others to measure or manage depression or bipolar illness.

In the world of hi-tech, behavior precedes proof. The scientific process of the academic world is slow, glacially so, compared to the practical process of the hi-tech world. Thus, many more apps will be available than are proven to be beneficial on scientific grounds. We will see how this process evolves. One important aspect is that Apple has developed an open free app platform called “ResearchKit” so that academic researchers can prove the benefit of different apps for medical conditions. If studies using those kinds of apps prove benefit, then clinicians in the near future may be in a position to be able to use those apps with their patients.

Most of that work is in non-psychiatric conditions, but interest is growing in psychiatric conditions like ADD and depression.

**Number 8: The opiate epidemic**

It is now clear that something has gone wrong with opiate prescription in the US. About a decade or two ago, the mantra was that physicians were being too Calvinistic, too conservative, in prescribing opiates for pain. The pharmaceutical industry benefited from, and helped spur, the campaign to prescribe opiates more liberally for pain syndromes. It is now clear that such increased opiate prescription has led to increased opiate abuse, and to intended and accidental deaths from overdose. This increase in mortality in younger populations has influenced the overall US population such that overall life expectancy in the US has plateaued for the first time in decades.

Some would say that we are in the midst of a public health emergency. Whether something will be done or not at the governmental level, and what, remains to be seen.

In the meantime, clinicians need to be aware of the extent of this problem and PL would encourage restricted and cautious prescription of opiate agents.

**Number 7: Binge eating disorder - A DSM-5 fad**

Many have criticized the DSM process for being too medical or biological, or being influenced by the pharmaceutical industry. While these specific criticisms aren't accurate exactly, in the PL view, there is reason for worry about such critiques in the case of this condition. Some have termed it “disease mongering”, that's when the profession creates a term that didn't exist before, and then the pharmaceutical industry markets it into the deep unconscious of prescribers.

This appears to be happening with binge eating disorder, which was included in DSM-5 for the first time in 2013, to the convenient profits of the makers of the amphetamine Vyvanse (lisdexamfetamine), who obtained FDA indication for the new DSM-invented label of BED in January 2015.

It isn't surprising that any amphetamine would reduce binging or any kind of overeating; this has been proven for over half a century. There isn't anything specific to Vyvanse for supposed BED.

One might ask how “BED” actually differs from overeating, but this kind of scientific question wasn't addressed in the DSM-5 process. As discussed in PL May 2016 issue, the DSM process is about “pragmatism” not science.
DSM invents a label. The pharmaceutical industry figures out how to make $5 billion a year from it.

PL urges readers not to fall for this disease mongering.

**Number 6: What should we do for adolescent depression?**

It is estimated that about 10% of adolescents reported a clinical depressive episode in the prior year, with most not receiving treatment. But what treatment should they receive? Typically they are treated with antidepressants, but as reviewed in PL October 2016 issue, those agents appear to increase suicide risk to a small but notable degree. Further, early onset depression in adolescence is the beginning of bipolar illness in about one-half of children, based on some studies. But the mental health profession is unwilling to diagnose bipolar illness in children and adolescents for cultural reasons, and even more unwilling to prescribe effective treatments like lithium or valproate.

The notable prevalence of adolescent depression is a problem that the mental health professions need to address more effectively. PL recommends a willingness to diagnose and treat bipolar illness in depressed children either when manic/hypomanic states have been present and/or when a family history of bipolar illness is present.

**Number 5: The first antipsychotic that is not a dopamine blocker.**

Rarely does a new medication for a kind of psychopathology involve a totally new mechanism of action. Pimavanserin (Nuplazid) is such an agent. It is now FDA indicated for psychosis in Parkinson's disease. It is a purely serotonergic blocker (being marketed as an “inverse agonist”, which seems to be the same thing as an antagonist). Prior research drugs that were pure serotonin blockers never made it to the US market because they didn't prove effective in schizophrenia. This agent was studied in Parkinson's disease, so it is unclear whether it will prove effective for psychotic symptoms in schizophrenia or mood illnesses, but if it turns out to be effective more broadly, it would be a key agent which would not have extrapyramidal side effects. We can wait to see how it will play out if further research is done in primary psychiatric conditions, and as clinicians get experience with it in Parkinson's disease.

**Number 4: Treat to remission?**

For about two decades, the teaching has been that clinicians should use medications to get rid of all symptoms, 100% of them, in conditions like depression and anxiety, if possible. Now we know that our antidepressants don't succeed at such complete remission in the vast majority of patients, even short-term. Some experts recommend doubling up, and giving more and more medications. PL recommends respecting the limitations of drugs, and thinking more carefully about which diagnoses we should treat with medications, and how far we should go. With multiple medications, further symptom benefit is minimal in almost 90% of persons with MDD, for instance, as shown in STAR*D, and yet side effects add up. The ratio of harm to benefit begins to veer strongly in the negative direction.

The Hippocratic tradition was about treating diseases, and not symptoms, otherwise much harm ensues. The obsession with removing all symptoms goes against that Hippocratic approach.
PL recommends more caution and more respect for the brain and body that is impacted by medications, all of which have some harms and side effects. Further, PL reminds readers, as described below, that such “resistant” symptoms sometimes reflect wrong or inadequate diagnosis, which is why ramping up of the same class of medications will not improve matters.

**Number 3: Is pharmacogenetic testing helpful?**

Some companies are now marketing pharmacogenetics testing to claim improved health outcomes. Most of these claims have to do with the serotonin transporter gene, the best studied genetic marker of treatment response for so-called major depressive disorder (MDD). Even if the claims are taken at face value, they often don’t acknowledge that they reflect only short-term benefits, meaning acute response for about 2 months. They don’t translate to long-term efficacy or treatment, although those companies usually want to presume so. Further, such claims don’t take into account the reality of misdiagnosis. As discussed on the PL website, about one-third or so of cases of “treatment-resistant” depression (TRD) involves simple misdiagnosis of bipolar depression, where antidepressants basically are ineffective (as discussed in PL January 2016 issue). TRD also can be understood as reflecting not ineffectiveness of the drugs, but ineffectiveness of the diagnosis of MDD. As discussed on the PL website, many different depressive conditions, often unresponsive to antidepressants (like mixed states), have been combined in the broad DSM-III based MDD concept. TRD can be seen primarily as a problem of diagnosis, not just the drugs. The pharmacogenetic world ignores all these matters.

**Number 2: Amphetamine stimulants are the most rapidly increasing prescribed class of psychotropic medications**

Recent clinical practice based data from the US indicates that amphetamine prescription is skyrocketing, unlike all other psychotropic drug classes, which are plateaued. It may not be a coincidence that most of the major antidepressants and neuroleptics and mood stabilizers are now generic medications, with no further major profits to be made by their manufacturers. In contrast, dextroamphetamine and methylphenidate are tweaked continually (lisdexamfetamine, Vyvanse; dexamethylphenidate, Focalin) so that pharmaceutical companies can continue to make immense profits. The related marketing ensures that the agents are prescribed.

PL July 2015 issue addressed the harms, including neurotoxicity, of these agents, as well as the questionable validity of the ADD diagnosis in adults, and sometimes in children. PL recommends that these agents be used much less frequently than is the case currently.

**Number 1: What will be the impact of legal marijuana?**

This is the question that the coming years will answer. Marijuana was legalized this year in a number of states. Will this legalization have a negative impact on substance abuse rates, or on psychiatric conditions that could be impacted by marijuana’s effects (such as depression and paranoia)?

There has been an impression, especially among the younger generation, that legalization implies safety. Of course, older generations remember that cigarettes always were legal. And alcohol is
certainly still a major public health problem, especially in young persons.

Mental health clinicians shouldn't assume the safety of marijuana either, and should be cautious when they are asked, as will be the case in many situations, to support marijuana use for anxiety or depressive benefits. Nicotine cigarettes also are anxiolytic, but that is not a reason to prescribe or condone cigarette smoking for that purpose.

Whatever social benefits may arise from legalization of marijuana, the medical effects of wider use of this agent are a different matter, and will require some attention.

**The PL Bottom Line for 2016**

- Internet addiction is a new burgeoning problem.
- Mental health apps aren't ready for prime time but will be important clinically soon.
- The opiate epidemic should influence clinicians to be more cautious with prescribing them.
- Binge-eating disorder is a classic case of disease-mongering. Clinicians should reject the marketing of Vyvanse.
- Adolescent depression is a major problem that isn't effectively managed by just prescribing antidepressants.
- A new antipsychotic that is not a dopamine blocker is now available, and could be promising if effective outside Parkinson’s disease.
- Don't treat to remission when symptoms are “resistant.” Think more carefully about diagnosis.
- Pharmacogenetic testing for depression ignores the problem of misdiagnosis and the heterogeneous and potentially invalid nature of the MDD construct.
- Amphetamines are the most rapidly increasing class of prescribed psychotropic agents, for better or for worse.
- The impact of legal marijuana on clinical practice is unpredictable.

**PL Reflection**

...the very concept of objective truth is fading out of the world....I know it is the fashion to say that most of recorded history is lies anyway. I am willing to believe that history is for the most part inaccurate and biased, but what is peculiar to our age is the abandonment of the idea that history could be truthfully written....It is just this common basis of agreement, with its implication that human beings are all one species of animal, that totalitarianism destroys....There is, for instance, no such thing as ‘Science.’ There is only ‘German Science,’ ‘Jewish Science,’ etc. The implied objective of this line of thought is a nightmare world in which the Leader, or some ruling clique, controls not only the future but the past.  

George Orwell
Winston Churchill used to say that every time a new book was published, he bought an old one. What is old has stood the test of time, at least in terms of books. If you wait a few years before you read what’s been published, you often weed out the temporary and insignificant.

There is a benefit to a longer perspective, so, as with last year, we provide another Top Five list of great insights from the history of psychiatry.

Just as a reminder, the 2015 list was as follows:

1. 1927: The first and only Nobel prize for a psychiatric treatment given to a psychiatrist was awarded to the chairman of the psychiatric department of the University of Vienna, Julius von Wagner-Jauregg, for malaria therapy of psychosis. Moral: The treatment worked for the highly prevalent psychotic disease of neurosyphilis, proving that careful clinical diagnosis in psychiatry can lead to biological cures.

2. 1954: A classic British textbook explains the problem of lack of insight. Moral: You can’t simply believe the patient about presence or absence of symptoms.

3. 1845: Esquirol, the great French physician describes how bleeding makes sense, but doesn’t work. Moral: Your treatments may make sense to you, but that doesn’t mean they work.

4. 1878: Daniel Tuke, a British physician, describes hypomania, mild manic symptoms, as important precursors of more severe states. Moral: Hypomania is an old and well-recognized idea, not a modern fad.

5. 1930: The historian Paul Roazen interviewed Freud’s ex-patients in the 1960s, one of whom (Dr. Imrita Putnam) recalled a 1930 psychoanalysis where Freud commented that psychoanalysis was “a fine thing for normal people.” Moral: Psychotherapies are wonderful, maybe more so for the normal than the sick, because “everyone has problems,” as Dr. Putnam said.

After this reminder of those five key lessons from the past, let’s turn to this year’s historical list.

Number 5: 1804 - Philippe Pinel develops “moral therapy” based on biological reductionism

Moral therapy is well-known, usually associated with removing physical restraints. One thinks of the paintings of Pinel, in the French revolutionary era, dramatically casting off the chains of the mentally ill in the famous Salpetriere asylum outside Paris.

It wasn’t actually that dramatic. Panel didn’t just treat people nicely, and suddenly they didn’t need chains anymore. Pinel’s methods were more complex. What he meant by “moral” therapy doesn’t have the same implications as the word as it is used now. It didn’t mean “ethical” as much as “rational” treatment. Pinel was a young physician who joined the young generation of Frenchmen who supported the French Revolutionary ideals of science and reason, as opposed to religion and monarchy. Before the Revolution, insanity was seen as a moral failure and/or as a reflection of sin, interpreted religiously. God was punishing the insane. Pinel rejected all such religious talk and emphasized that insanity reflected disease of the body and brain (just as Hippocrates had claimed in the pre-Christian era), and thus it needed to be
treated humanely, since it didn't reflect sin of any kind.

In other words, Pinel was a biological reductionist; that's why he was a humanist. He didn't have effective treatments, and he knew so. But he also knew that the diseases of insanity could be divided basically into two groups: those which recovered naturally (episodic) and those which did not (chronic). In the case of the first conditions, humane care could be given until nature cured the disease. In the second case, humane care would be needed in a more prolonged fashion, since cure would never occur.

Pinel's classic textbook on insanity was revolutionary because it took this biological approach to psychiatry, with its humane and “moral” implications. In that era of the Enlightenment, science and humanism went hand in hand, contrary to many of our current postmodernist assumptions otherwise.

The moral: Biological psychiatry can be, and was, very humanistic.

**Number 4: 1949 - John Cade discovers lithium.**

John Cade was an Australian psychiatrist who developed the idea of lithium as being effective for psychiatric conditions while interned in a prisoner of war camp in the Second World War. His initial thought was that the active ingredient was the compound combined with lithium, namely uric acid. But lithium urate had the same effects as lithium carbonate, and Cade drew the conclusion that the active ingredient was lithium. First, he gave those agents to guinea pigs (literally), and then to himself (true), and then to about a dozen patients. He published his case series in Australia, a paper that likely would be rejected in most scientific journals today (case series are very unpopular and considered “anecdotal”). Within a few years, the first randomized trials in psychiatry would be conducted with lithium, and would prove Cade right.

Nonetheless, there was great resistance, especially in the British leaders of psychiatry (like Aubrey Lewis and Michael Shepherd) to the idea that lithium worked for manic-depressive illness. It wasn't until 1970, a generation after the initial discovery, that lithium became available on the US market.

The moral: Perhaps the most effective medication in psychiatry was discovered in a few cases by an active clinician, not a prominent academic, and resisted by the psychiatric establishment for decades.

**Number 3: 1975-80 - Thomas Wehr, Frederick Goodwin, and Athanasios Koukopoulos discover that antidepressants can worsen bipolar illness**

Some PL readers may know that the PL editor has worked with the psychiatrists mentioned above on this topic, but that personal relationship notwithstanding, it is worthwhile noting that it was in this time that antidepressants were noted to have some negative effects in bipolar illness. They caused mania, and, more controversially, they worsened rapid-cycling, causing more and more depressive and manic episodes over time. Wehr and Goodwin first published their observations in 1975, based on careful study of a few patients at the National Institute of Mental Health, and they followed it up with a randomized trial supporting their observations. Similar findings were published by Koukopoulos and colleagues based his active clinical practice in Rome.

PL readers know the topic remains controversial and clinical practice has not changed much since
the 1970s, with antidepressants remaining widely used in bipolar illness, as discussed in February 2016 issue.

The moral: Clinicians accept benefits of medications much more quickly than they admit potential harms.

Number 2: 1946 - Viktor Frankl publishes “Man’s Search for Meaning”

There are profound and superficial ways of assessing the importance of Frankl’s masterpiece. The superficial one is that it is still widely read 60 years after it was written. The profound one is that it is one of the few books in psychiatry that speaks directly to all people about basic human dilemmas. It’s worthwhile noting that its original title in German translated to: “Nevertheless, Say ‘Yes’ to Life: A Psychologist Experiences the Concentration Camp.” Its first English translation in 1959 was titled: “From Death-Camp to Existentialism.” Frankl was a psychiatrist from Vienna who had trained in psychoanalysis in the 1930s under Freud's first prominent pupil, Alfred Adler. Frankl was not an intimate of Freud himself, though living in the same city, but he had learned psychoanalytic ideas from the source. When he was interned in the Nazi concentration camps, he observed that much that he had learned in his psychoanalytic training was of little use. He observed that most of his fellow inmates didn't dream about sex or aggression, but rather about food. They didn't yearn to satisfy their sexual or aggressive instincts, but rather merely to survive. He observed further that those who survived were those who suffered. Those who perished were those who could find no meaning in their suffering. Apathy - the loss of all emotion - was the worst outcome, much worse than the despair of unremitting anguish. At least in despair, one experiences an emotion; one is still alive. When all emotion is gone, one dies, first mentally, then physically. This is one of the insights that Frankl described so well, and which led him to move away from psychoanalysis and towards a new approach, existential psychotherapy, a way of thinking that had been started by Karl Jaspers.

In a way the concentration camps were the ultimate - immoral - test of the psychoanalytic hypothesis as opposed to other approaches to understanding human existence. Freud's thinking, for all its insights, failed to be sufficient. Another approach, existential psychiatry, seemed more adequate.

Number 1: 1913 - Karl Jaspers publishes General Psychopathology

Around the turn of the century, Emil Kraepelin, the great German psychiatrist, became chairman of the department of psychiatry at Heidelberg, one of the most prominent universities in Germany. A few years after he moved onto Munich, a young resident entered the program. Karl Jaspers learned Kraepelin's objective-descriptive approach to psychiatry well. Jaspers also studied and learned about a new thinker in the field, Freud, who taught of the importance of the subjective meaning of psychological experiences. These two approaches conflicted, and Jaspers sought to find a way to make sense of the best approaches to psychiatry. He came upon a way of thinking that can be seen as scientific thought applied to psychiatry; he called it “methodological consciousness”, by which he meant that different methods in psychiatry have different strengths and weaknesses. No single method is the best or explains everything. Thus, Kraepelin's approach made sense for severe psychotic or affective diseases, while Freud's approach worked in traumatic neuroses. One approach wasn't inherently better or worse; it depended on what they were being used to study.
or treat. In addition to this central conceptual insight, Jaspers himself developed a third method: he called it “phenomenology”, and it has come to be called the existential-phenomenological approach in psychiatry. Jaspers went on to work as a philosopher most of his life, and founded the school of existentialism in philosophy (along with his colleague, initially a friend and later an enemy, Martin Heidegger). The existential approach (if we may shorten the title thus) is a method that is valid in psychiatry to address all patients as human beings. It views everyone in terms of the basic human dilemmas we all share, and the limits we all experience that cause sadness or despair. Many life problems come to psychiatrists where neither psychotic nor affective diseases are present, nor are there traumatic neuroses. In such settings, Jaspers offered a new approach centered on the method of empathy, a concept first advocated by Jaspers and now taken for granted and often understood superficially. These ideas were best laid out in his classic text General Psychopathology, which he published in the final year of his residency training.

For those readers who wish to read more about Jaspers’ ideas, a more readable and less daunting source is “Way to Wisdom,” which is a summary of his philosophy given as radio lectures in the 1950s. Though it isn’t directly about psychiatry, it lays out Jaspers’ basic thinking in general, and the links to psychiatry can be seen in many places.

**The PL Bottom Line**

- The humanistic approach in modern times in mental health was linked to biological psychiatry.
- The greatest drug discovery in psychiatry, lithium, was based on a few cases observed by an astute clinician, not a complex large university-based research study.
- Clinicians are more likely to accept research that shows benefits with medications as opposed to harms.
- The concentration camp experience failed to validate psychoanalytic ideas, but supported existential approaches.
- Empathy was promoted by Karl Jaspers as the core method of the existential approach to psychotherapy.

**PL Reflection**

The death rate in the week between Christmas, 1944, and New Year’s, 1945, increased in camp beyond all previous experience....It was simply that the majority of the prisoners had lived in the naive hope that they would be home again by Christmas.... Nietzsche’s words, ‘He who has a why to live for can bear almost any how,’ could be the guiding motto for all psychotherapeutic...efforts regarding prisoners. Whenever there was an opportunity for it, one had to give them a why - an aim - for their lives, in order to strengthen them to bear the terrible how of their existence. Woe to him who saw no more sense to his life, no aim, no purpose, and therefore no point to carrying on. He was soon lost....What we really needed was a fundamental change in our attitude toward life...that it did not really matter what we expected from life, but rather what life expected from us. We needed to stop asking about the meaning of life, and instead to think of ourselves as those who were being questioned by life - daily and hourly....

Viktor Frankl
Current Study of the Month: Predicting depression in kids

Antecedents of New-Onset Major Depressive Disorder in Children and Adolescents at High Familial Risk. F. Rice et al, JAMA Psychiatry. Published online December 7, 2016.

A new study confirms that in children anxiety precedes depression

In prior PL issues we raised the idea that anxiety is the fever of psychiatry. It is more often an effect than a cause. It happens for a hundred reasons. In this newly published paper, we read about another aspect of anxiety: It is the nonspecific expression of psychopathology in children, before more specific conditions like mood diseases or schizophrenia become apparent.

In this study, 304 children (aged 9-17 years) of depressed parents were followed prospectively for four years. 20 children met MDD criteria in follow-up. Anxiety and irritability at baseline predicted later development of clinical depression, but disruptive behavior and low mood did not.

Anxiety is like fever in infections. If a patient has HIV, with a high fever, and complains terribly about the fever, and the fever is so obviously a problem, it doesn't follow that the main attention in diagnosis or treatment should be given for the fever. This doesn't mean that the fever is to be ignored, but only that its symptomatic treatment with Tylenol is only partially important. Treating the underlying cause of the fever - the infection - is even more important.

So it is with anxiety in psychiatry, especially in children. The child or adolescent presents with terrible anxiety; the parents complain bitterly about it. The serotonin reuptake inhibitors are available to treat the anxiety symptomatically. The prescription follows. But this decision doesn't get at the cause. This study shows that anxiety is a common early presentation of recurrent depressive illness in children and adolescents. It's not that the anxiety “causes” the depression, but rather that the mood illness presents initially as anxiety, and later as depression. It's the same disease from day one, when the child is born; the genes are the same and they are expressed in the brain developmentally such that anxiety follows first, and then depression. In the end, though, it is a disease of mood, with anxiety as an early presentation. These clinical presentations aren't the disease itself - which is the biological abnormality in the brain - but rather they are the effects of the disease.

As noted earlier, also, apparent “MDD” in children is not just MDD since early-onset depression was the hallmark of bipolar illness, and the whole concept of MDD was based on the idea that it began later in life, around age 30. As discussed on the PL website, about one-half of children with depressive episodes only (supposed MDD) later have manic or hypomanic episodes (and thus have bipolar illness). Hence, the simple prescription of SRIs for anxiety in such children is not risk-free, given the risk of causing mania or worsening the course of the mood illness. This effect may underly the increase in suicidality caused by SRIs.

Irritability can be seen as a manic symptom, and it too predicted depression. These observations all are in line with the traditional concept of manic-depressive illness, as described on the PL website.
**Curbside Consults**

*Questions and cases from you*

**Question:** I have learned from *PL* that diagnostic validators, like course and family history, are essential to diagnose manic-depressive illness. A question arose for me on this topic in relation to a new patient I saw recently. He is a man in his mid-30s, dismissed from his military job a few years ago. He presented to our hospital with severe paranoid delusions, along with psychomotor retardation and social withdrawal.

Past psychiatric history identified a severe depressive episode with serious suicide attempt by firearm at age 27. His father described three clear manic episodes (lasting over a week each) in the following years, alternating with more frequent depressive episodes. Military service likely exposed him to some head trauma. Family history identified a similar condition in a paternal uncle, with age of onset of 30 years.

My question: How do we explain this relatively late-onset of manic-depressive illness in the patient (late 20s) as well as his uncle (age 30)? Is it due to genetic anticipation? Or is it secondary to head trauma or a schizoaffective condition?

**PL:** Thank you for this thoughtful clinical evaluation. As you know, the mean age of onset of bipolar illness is about 20, while for unipolar depression it is about 30. But this is an average, with a normal curve to each side of this peak. Certainly 5-10 years would be a reasonable range on either side of the average, which means that bipolar illness begins in the range of 10-30 years of age, with 20 being the average. (Similarly, unipolar depression can be seen as occurring mainly around age 20-40, with 30 as the mean).

Thus, the onset of late 20s in this case, though less common than an earlier age, is consistent with the usual course of bipolar illness. Further, it should be noted that the first depressive episode was quite severe. It is possible that the patient had milder to moderate clinical depressive episodes earlier in life which he and his family may not have noted, but which would establish an earlier age of onset. Finally, about one-half of such patients have an affective temperament. In the PL view, the age of onset is when the affective temperament starts, not when the first mood episode occurs. In other words, some patients have their first depressive episode in the 40s, 50s, 60s, or even later, but they had cyclothymic or hyperthymic all their lives, from childhood onwards. In such cases, the official age of onset of the mood disease is late, but the actual onset of the affective condition is in childhood with the affective temperament.

Given these considerations, the case is within the range of typical for manic-depressive illness. That said, there is some evidence for genetic anticipation in some families with bipolar illness, with earlier age of onset with succeeding generations. This family doesn't follow that pattern though.