

THE PSYCHIATRY LETTER

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The End of the Beginning

This issue represents the end of the first year of the existence of this newsletter. We would like to thank you who are reading these lines in the weeks after its publication because you have been a loyal and sympathetic audience for this effort.

This newsletter has gone from crawling to walking and we hope to see it off and running into the future. We hope you stay with it into its second year of existence and beyond.

As noted in the last issue, an exciting aspect to this second year of life for PL is the ability to provide Continuing Medical Education (CME) and Continuing Education Units (CEU) to our readers. This will apply to psychiatrists and nurses and psychologists. Our next step will be to obtain CEU accreditation for social workers; we will notify you when we have obtained such accreditation.

In honor of the first year anniversary of the newsletter, which coincides with the end of the old year and the birth of a new year, the December newsletter is a special issue with a Top Ten list of events, studies, and topics in psychiatry in the past year.

In the next issue, January 2016, we will return to our usual format, with, for the first time, CME/CEU credit availability. We hope you take advantage of those credits for your needs.

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 2015

Our review of key topics in psychiatry this year

The New Year reviving old Desires
The thoughtful Soul to solitude retires
Where Jesus upon the Bough puts out
And Moses from the Ground suspires.

Omar Khayyam (adapted by Edward Fitzgerald)

What's important?

At the beginning of a new year, and the end of an old, PL turns to the tradition of thinking about what happened in the past year and identifying the most important topics or debates or studies in the mental health professions. In so doing, PL defines what is important not necessarily as what is right or what PL thinks matters, but rather what has been in public discussion. In this review, PL provides its perspective frankly, not necessarily with all the evidence for its conclusions. On the PL website and in PL issues cited, relevant links are provided to articles which provide further elaboration.

"...Ketamine is addictive in animal studies. It also is neurotoxic, causing neuronal cell death in animal studies."

Number 10: How effective is ketamine?

Recently, many clinicians have been swept away with enthusiasm for ketamine, a NMDA receptor antagonist. This drug, which is mainly used in intravenous form, had been part of traditional anesthesia treatments for many years. When given to patients with treatment-resistant depression (TRD) or bipolar depression, some small randomized trials have reported benefit for the acute clinical depressive episode. The main claim was that IV ketamine produced "rapid" response within days to weeks, unlike traditional oral monoamine agonists, which require weeks to months for efficacy.

To PL, this "rapidity" of response is uninteresting. The problem in the treatment of the vast majority of patients with depressive conditions is not that response is too slow; the main problem is that response occurs acutely but is not maintained for the long-term. (See the PL website for a discussion of the STAR*D study which is the basis for this judgment). There is NO evidence of any long-term benefit with ketamine, and certainly not in randomized comparison to other proven effective alternatives like lithium.

Thus, the PL view is that ketamine is much ado about nothing.

Many are beginning to identify and decry the rise of "ketamine clinics", often staffed by physicians who are not mental health professionals, with profits from out of pocket payment by patients.

Even if ketamine worked in any important manner, its intravenous use would hamper its practical utility. Some clinicians have taken to intramuscular or even intranasal administration. These uses are unproven.

A final point: Ketamine is addictive in animal studies. It also is neurotoxic, causing neuronal cell death in animal studies. Human studies are few in number, varied in result, and do not outweigh the animal data.

It is understandable that many patients and clinicians want a simple solution to a complex problem. The problem: Many patients with DSM-defined "major depressive disorder" (MDD) do not respond to standard "antidepressants." The simplistic solution: Get a better antidepressant.

The alternative solution: Get a better diagnosis than MDD, which is unscientific in its core, as discussed on the PL website, and then we might find that many of our available drugs can work quite well, short and long-term, for more scientifically valid definitions of depressive conditions.

As for ketamine: It is likely that it sounds too good to be true because it is.

Number 9: Do benzodiazepines cause dementia?

A study in the past year reported that benzodiazepines were associated with increased risk of dementia. As reviewed in the May 2015 PL issue, this conclusion is not definitive since the study was observational, not randomized. Thus, many confounding factors could have influenced the result. The study controlled for many of those confounding factors but it could not control for all of them. The interpretation is less straightforward when we add in the fact that a number of animal studies show the opposite, namely that benzodiazepines are neuroprotective and keep neurons alive longer.

The PL verdict: Clinicians need not make major decisions yet on whether or not to use benzodiazepines, especially in older persons, on this possible association.

Number 8: How can we stop suicide in soldiers?

It is now a well known statistic. Every hour, a US soldier back in civilian life kills himself. Why is this happening? How can we stop it? A number of major Veterans Administration funded studies have looked at this matter, one of which was reviewed in the August 2015 PL issue. Obviously

PTSD is the main culprit, but associated factors are present which increase the risk of suicide in some veterans versus others. The fact that veterans have been trained to kill and are expert with firearms certainly is a key general risk factor.

In the larger literature on PTSD, PL emphasizes the importance of personality traits, factors which are present in individuals before, during, and after war-related trauma. Depressive and anxiety traits increase the risk of PTSD; manic traits decrease the risk of PTSD. Thus, if soldiers have dysthymia or high neuroticism as part of their personality, before going to combat, they are more likely to have severe PTSD upon their return. In contrast, those with hyperthymic temperament are less likely to have severe PTSD upon return.

How is this relevant to preventing suicide in veterans?

“Lithium is the only drug proven to prevent suicide.”

One aspect would be more attention to affective temperament in the screening of civilians who want to enter the military. Currently, systematic assessment of affective temperament does not occur in psychiatric evaluations of those entering the military.

Number 7: Use lithium to prevent military suicide

Another important solution to this devastating problem of veteran suicide deserves its own separate place on the Top Ten list. This topic has been ignored by policymakers: Lithium is the only drug proven to prevent suicide. It should be given more widely to veterans with suicidal ideation. It can be effective for suicide prevention even in low doses, according to some data, like 300 mg/d or even less. Thus, it can be given in tolerable dosing to almost anyone.

PL has come to this conclusion regarding lithium for suicide prevention: There is no minimum effective dose. Thus almost everyone should be able to take it.

Number 6: Diabetes is a major risk factor for dementia.

Recent studies have found a strong correlation between diabetes and dementia, with more than a doubling of risk. This kind of effect has also been found in the past with depression as a risk factor dementia.

These observations are clinically important. Clinicians frequently give olanzapine or quetiapine, the most common dopamine blockers that cause diabetes, to middle aged persons, who enter their 50s and 60s with increasing risk of dementia. The iatrogenic causation of diabetes with these agents will multiply the long-term risk of dementia in such persons.

Often those agents are used to treat depressive symptoms, but other dopamine blockers, like aripiprazole and ziprasidone, can do so without risk of causing diabetes.

Number 5: Should we be more active in diagnosing and treating adult ADD and binge eating disorder and DMDD?

Here PL lumps together a number of invented DSM-5 diagnoses, which have been reviewed in prior issues on the PL website. The PL judgment is that these purported diagnoses have little to no scientific validity, and thus their diagnosis and treatment is not a scientifically meaningful process. Readers will note that the treatments for adult ADD and binge eating disorder mostly involve amphetamines, which provide symptomatic benefit in both cases but this benefit also occurs in normal populations (everyone

concentrates more and eats less with amphetamines). Hence such “benefit” does not imply diagnostic validity. As reviewed in detail in the October 2015 PL issue, and on the PL website, amphetamines also are harmful with neurotoxicity, meaning causing neuronal death, in animal studies, without clear confirmation or refutation in the limited available human studies.

Regarding dysphoric mood dysregulation disorder (DMDD), a publication after DSM-5 noted that there had never been any study of its prevalence or diagnostic validity or treatment. The concept was invented to discourage clinicians from diagnosing bipolar illness in children. Separately from where readers stand on whether and how bipolar illness should be diagnosed in children, PL feels that it is not a scientific process to invent one purported diagnosis to prevent clinicians from making another one. Future issues will address the controversial topic of childhood bipolar illness.

“Be cautious about all dopamine blockers and neurotoxicity”

Number 4: Do antipsychotics harm the brain?

Yes, they do, according to human studies in the past few years. Those studies mostly involve traditional dopamine blockers, like haloperidol, and many experts state or assume that new dopamine blockers will not have that risk. They often cite animal studies which report neuroprotection with newer dopamine blockers. Those animal studies often are conducted by the pharmaceutical companies that produce those agents. Because of the problem of non publication of negative studies, we cannot know how many animal studies have been conducted by pharmaceutical companies which show neurotoxicity with their dopamine blockers. They are under no obligation to publish those studies.

The PL verdict: Be cautious about all dopamine blockers and neurotoxicity. The older ones now are known to cause that effect, the newer ones have neither been proven nor disproven to do so.

Is this a reason NOT to prescribe dopamine blockers? No. Even with the older agents, the chronic psychotic illness of schizophrenia was associated with more neuronal damage than was associated with the dopamine blockers. In other words, the drugs are harmful somewhat to the brain, but the disease is even more harmful.

Number 3: Do antidepressants work?

As reviewed in detail in PL website, the PL verdict is as follows:

Antidepressants work. MDD doesn't work.

The problem is not that “antidepressants” don’t work in general, or are marginally better than placebo in general, which is what the anti-psychiatric critics claim. The issue is not a general one at all. The important factor is that antidepressants work better for certain kinds of depressive presentations, and less for other ones. This is because MDD is a mixture of many kinds of depressive conditions, and when we lump together the higher and lower amounts of antidepressant benefits for the many depressive conditions mixed up in MDD, we get a “marginal” overall effect, which is clinically meaningless. What is important clinically is to better identify depressive conditions so that we can target antidepressants more effectively.

As reviewed in February 2015 PL issue, monoamine agonists (a better term than antidepressants) are NOT effective in mixed depression, and are less effective in melancholic depression. They are effective in neurotic

depression, but not more so than placebo. In other words, those patients always improve to some extent, whether or not they receive monoamine agonists. These medications are effective acutely in depression that is not mixed, not melancholic, and not neurotic, in other words, in fewer cases than are commonly assumed. Long-term preventive efficacy also is less well-established than is appreciated by many clinicians. Future PL issues will examine the STAR*D study and other data to explicate this topic.

Number 2: Light boxes aren't just for winter.

A fascinating randomized trial found that the use of a light box was effective for the acute depressive episode in persons who did NOT have seasonal depression. In fact, light box treatment was more effective than fluoxetine (Prozac) acutely. This finding raises the new possibility that light boxes could be used for acute depression treatment even outside of classic fall/winter depression. PL urges caution with the fact that if used in the spring and summer, in susceptible persons, light box therapy can cause mania, like any antidepressant treatment.

Number 1: Should we be excited about the human genome project and genetics?

“Personalized medicine” is the slogan of current health care policy. Everyone is talking about it. In medicine, uses are focused mostly on oncology, which we can hope will produce more effective treatments. The question has been raised whether this research is able to produce any benefit in psychiatric conditions, with most focus being on schizophrenia and bipolar illness and

“What is important clinically is to better identify depressive conditions so that we can target antidepressants more effectively.”

“MDD”. Many experts and clinicians are hopeful for a pharmacogenetics breakthrough.

Miracles have long been awaited in our field, as the historical insights section below will remind us. This is not to say that this work in pharmacogenomics isn't useful, but only to say that we should be cautiously optimistic.

The PL concern regarding MDD returns to the problem of DSM-5; if the diagnosis is based on social and professional judgments, not scientific ones, we can't expect genetics to follow the profession's lead.

So far, a few disease genes have been replicated in schizophrenia and bipolar illness. Little progress has occurred with MDD, which PL would expect to be the case.

Treatment predictor genes may have some promise, if disease states are identified more validly. PL hopes that future research will produce such genetic predictors. So far, none are on the horizon, but we will keep our eyes open in the new year and years to come for any future advances.

The PL Bottom Line for 2015

- Ketamine probably is not going to prove to be clinically useful.

- Diabetes is a major preventable cause of dementia, especially when related to some antipsychotics.
- Benzodiazepines, in contrast, are not major or clear risk factors for dementia.
- Use a light box in any kind of acute depression, but beware of mania.
- Veterans are more likely to develop PTSD if they have depressive affective temperaments, and less likely if they have manic affective temperaments.
- Use low-dose lithium to prevent suicide in veterans.
- Dopamine blockers probably are neurotoxic, especially the older ones, but this does not entail stopping their use in schizophrenia.
- New DSM-5 diagnoses that are not scientifically valid should not receive clinical attention.
- Antidepressants “work” in the right kinds of depression, but not other kinds.
- Genetic research will not provide a miracle around the corner, but, combined with more scientifically valid diagnosis, one can hope for some progress in predictors of treatment response.

PL Reflection

Is not disease the rule of existence? There is not a lily pad floating on the river but has been riddled by insects. Almost every shrub and tree has its gall, oftentimes esteemed its chief ornament and scarcely to be distinguished from the fruit. If misery loves company, misery has company enough. Now, at midsummer, find me a perfect leaf or fruit.

Henry David Thoreau

Special Article II: Historical Top Five List

Other years, once new, teach us some old lessons

Every year we focus on the 12 months that passed. A longer time horizon can provide a better focus, perhaps, about insights that have stood the test of time, not just for one new year but for many many years. In this article, PL analyzes a Top Five list of insights from the history of psychiatry.

Number 5: 1927 - The first and only Nobel prize given to a psychiatrist for a psychiatric treatment

PL Note: Julius von Wagner-Jauregg was a medical school classmate and for a time a research colleague of Sigmund Freud. While Freud struggled in private practice, Wagner-Jauregg rose quickly in academic stature to become chairman of the department of psychiatry at the University of Vienna. In later years, though they opposed each other on many occasions (including in court), they had qualified respect for each other, exchanging birthday greetings yearly. Throughout his life, Freud hoped to obtain the Nobel Prize, for which he was nominated but rejected. Wagner-Jauregg, now forgotten, obtained the prize for malaria therapy for neurosyphilis, a treatment that seems odd to us now, but had, in fact, an important historical impact on psychiatry, mostly for the better. Historian Edward Shorter (*A History of Psychiatry*, pp 194-196) tells this story:

In 1883, during his residency at the asylum, Wagner-Jauregg noted that a female patient who had contracted erysipelas, a streptococcal infection, experienced a remission of her psychosis. This piqued his interest in the relationship between fever and madness, which had long been a subject of medical inquiry. In 1887, Wagner-Jauregg wrote an article speculating that it might be possible to treat psychosis through the use of fever. He mentioned neurosyphilis as being potentially treatable....

In 1890 the German microbiologist Robert Koch developed a vaccine, tuberculin, that was supposedly effective against tuberculosis. Wagner-Jauregg injected tuberculin into several patients whose psychotic symptoms were caused by neurosyphilis, with the aim of giving them a tuberculous fever. (It was thought that fever itself arrested the progress of neurosyphilis on the ground that the syphilis spirochetes are heat-sensitive). By 1909 he was regularly obtaining long-term remissions of the symptoms of neurosyphilis through the use of tuberculin. Yet he discontinued his experiments with tuberculin because it was considered to be toxic.

Wagner-Jauregg then returned to the possibility of giving paretics a fever with malaria, which, unlike other possible infections, had the advantage of being controllable with quinine. In June 1917, he learned that one of his patients, a soldier sent back from the Macedonian front with shell-shock, seemed to have malaria. An assistant physician asked Wagner if the patient should be given quinine. No, said Wagner, who decided upon the spot to inject some of the soldier's blood into his neurosyphilitics.

In May 1917, a 37 year-old actor with the initials T.M. had been readmitted to the clinic with the now advanced symptoms of neurosyphilis, including weakness of memory, fits, and pupils that were unequal in size and unresponsive to light, a clinical picture that customarily amounted to a death sentence. There being nothing to lose...Wagner-Jauregg inoculated T.M. with malaria. Three weeks later, the patient had his first febrile attack, and after nine such attacks was given quinine. Astonishingly, after the sixth

"...neurosyphilis...a clinical picture that customarily amounted to a death sentence"

malaria attack, the syphilitic fits came to an end. [Wagner-Jauregg later wrote]: 'In the course of the following months, there was gradual improvement to the point of abolition of all of the patient's symptoms...' A year later Wagner-Jauregg gave the first report of his work, describing the effect of the malaria-cure upon a total of nine patients. This was an epochal moment... Wagner-Jauregg's fever "cure" (it did not cure but it did restore an almost normal life to patients who otherwise would have died demented) broke the therapeutic nihilism that had dominated psychiatry in previous generations. If one could halt the neurosyphilitic psychoses, perhaps psychotic illness from other causes was treatable as well. Wagner-Jauregg received the Nobel Prize for this work in 1927.

Number 4: 1954 - Don't believe the patient.

PL Note: The most widely read psychiatric textbook of the mid 20th century was *Clinical Psychiatry*, written by three British psychiatric academic leaders, two of whom were of Continental origin. Willy Mayer-Gross from Germany and Martin Roth from Austria (both influenced by the great German psychiatrist Karl Jaspers) had emigrated and worked in the UK for most of their adult lives. Together with Eliot Slater, they produced, in the opinion of the PL editor, the most comprehensive and clear-headed psychiatric textbook of the last 50 years. The last edition, published in 1969, predates most of the new medications, which would lead later generations to forget about this treasure trove of psychiatric wisdom. This excerpt (p 36) gives a taste of their insights into the psychiatric interview:

"It is even more important to know what the facts are than to know what the patient makes of them."

Only in the course of time can the psychiatrist develop the art of eliciting by tactful questioning all he has to know. Long training is needed to learn how to overcome the patient's resistance, to be aware of where his tale is biased, where information has been withheld and where it has been coloured by an emotional attitude. The

beginner is inclined to take every statement the patient makes at its face value. In this he has been encouraged by psychoanalytic teaching that fabrications and even deliberate falsifications have their value as symptoms. He must, however, beware of an *uncritical credulity*. It is the objective world in which we live and to which the subjective world must pay deference. It is even more important to know what the facts are than to know what the patient makes of them.

Number 3: 1845 - Your treatments may make sense to you, but that doesn't mean they work.

PL Note: For two millennia, almost all physicians agreed that bleeding was an appropriate treatment for almost all conditions, including insanity. This was based on widespread acceptance of the four humor theory of disease. Here we have a good description of the state of the art in the mid 19th century, written by Esquirol, a successor to the great Philippe Pinel of Paris, founder of the moral therapy approach to insanity which led to removal of chains. Pinel's humanism was based on a biological theory of insanity being a disease of the brain, and thus he taught skepticism about the widespread bleeding which was the accepted mainstream standard of care of two thousand years. Yet even in his circle, bleeding and other evacuations predominated, as described in Esquirol's textbook, *Mental Maladies* (pp 404-405). As you read about these treatments, widely accepted by the most advanced clinicians of that era, think about what treatments these days are accepted widely and yet may prove to be mere beliefs as opposed to scientific facts:

Administration of medicines...calls for careful reflection...So easy it is for us to permit ourselves to be imposed upon by the violence of symptoms. The same medicines should not be ordered indiscriminately to all maniacs and during all periods of the malady....

At the outset of mania, during its first symptoms, if gastric symptoms are present...we may employ

emetics....If indications of plethora are present, we employ and repeat blood-letting. We apply leeches behind the ears, or upon the temples; cupping glasses to the back of the neck; and frequently a small number of leeches to the anus.....

We must be cautious respecting sanguine evacuations. By enfeebling maniacs, we run the risk of throwing them into dementia. 'Bleeding,' says Pinel, 'is an unusual evacuation....How numerous are the maniacs who have never lost blood, and been cured; how many have been bled, but still remain incurable!'

We employ tepid baths, and continue them for two, three, and four hours; repeating them two and three times a day, by giving a bath every time that the delirium and fury is renewed, if the subject is of a dry and irritable temperament. While the patient is in the bath, we apply cold water constantly to the head...We insist upon the use of cold, diluent and slightly laxative drinks. Lastly, we unload the large intestine by enemata, at first emollient, then purgative. The diet should be cautiously restricted.

Number 2: 1878 - Pay attention to mild symptoms, even hypomania.

PL Note: Daniel Tuke was a British physician whose treatise on mental illness, *Insanity in Ancient and Modern Life*, is full of insights that still ring true today. Here he describes the importance of paying attention to mild mood symptoms, especially hypomanic ones. These days, many clinicians use the term "hypomania" as a way to minimize the importance of manic-depressive disease, as if manic symptoms only matter when they are severe. Tuke reminds us that mild manic symptoms are important to diagnose:

Warnings of danger are very frequently, if not always, associated with the inability to sleep. The

foe is insidious, and, true to his character, loves to assail us in the dark. He comes upon us in the night....

Emotional warnings there are also, which are of grave import, and ought to be regarded with suspicion by those to whom they occur. Among these may be enumerated slight depression of spirits, especially if this alternates with a sense of exaltation and buoyancy...The buoyancy of spirits...is less likely to excite apprehension among friends than despondency; but it is most important to remember that exuberant spirits, mental exhilaration, loquacity, when unusual to the individual, are fully as serious indications as are the opposite states of mind....

Unfortunately, when action is taken, mistakes in business have been made, or legal documents have been signed which involve serious consequence, family disputes have been occasioned, friendships have been broken, and a great deal of misery caused in various ways, all of which might have been prevented by arresting the symptoms by timely treatment, or failing this, arresting the patient himself and sending him to an asylum in an early stage of the disorder....

Number 1: 1930 - An analysis with Freud was "a fine thing for normal people"

PL Note: The historian of psychoanalysis, Paul Roazen, had made it his business to identify and interview all of Freud's living ex-patients in the 1960s and 1970s. In his book, *How Freud Worked*, Roazen brings Freud the clinician to life, and reveals some astonishing facts about what he believed and how he practiced. Here is an excerpt of the experience of one of Freud's ex-patients, herself a psychoanalyst, as interviewed by Roazen in 1966 (pp 167-187):

Dr Irmarita Putnam...struck me as one of the most unusually detached and brainy of all the former patients of Freud's that I ever

met....Although Dr. Putnam had once been a practicing analyst in Boston, by the time I had met her she was 71 years old and living in a quietly elegant New York City apartment....In 1925 Dr. Putnam spent not quite a year in analysis with Jung...Thinking back on her contact with both Jung and Freud, Dr. Putnam thought that ‘one could not have imagined any two people more different.’

[By 1930 she had arranged therapy with Freud himself]. She felt Freud was very attentive, as if she were his ‘first patient.’ While she was in treatment with Jung, he had wanted to talk primarily about what he was interested in....Freud was ‘different’; he talked about ‘everything under the sun’ - but he ‘analyzed’ her ‘too’....Although the analysis was never lost sight of, a great deal else came into the picture. He spoke about Communism and opera, for instance....Yet the analysis was undertaken in the ‘strictest’ fashion; there was nothing ‘social’ about it, and only what was relevant got introduced....

Dr. Putnam knew that Freud had been disillusioned with his early analyses, which had once looked so successful but had turned out not to be. He talked about having become skeptical himself, especially about the therapeutic value of psychoanalysis....When something happened in Dr. Putnam’s analysis that was ‘classical’, he would say, “Didn’t I tell you that psychoanalysis was a fine thing for normal people,’ and he would laugh....

Dr. Putnam felt in the course of her own analysis that everything was her own responsibility, and she did not resent what Freud expected of her. Before she saw Freud it had never occurred to her not to ‘project like other people,’ seeing in others her own weak points. The lesson she took away from her psychoanalysis with Freud was that you should not find faults elsewhere, but rather be preoccupied with what you yourself are doing. Even if the other person was in the wrong, what counts is what you are able to do with the situation. She had the healthy-minded conviction that ‘anything can be made somewhat better or worse....’

I asked Dr. Putnam if she thought she had been helped by her therapy with Freud, and her answer was unequivocal: ‘Definitely.’ He had considered her ‘normal,’ but she of course, like everybody, had ‘problems.’

The PL Bottom Line

- Psychosis can be cured.
- Don’t believe what the patient says at face value.
- “Standard of care” treatments can be false.
- Hypomania is not innocuous; mild manic symptoms are diagnostically and therapeutically important.
- Psychoanalytic therapy may be most helpful to normal persons.

PL Reflection

We do go about curing a substantial number of ailments...But there is another part of the mystique. It's the great secret of doctors, known only to their wives, but still hidden from the public. Most things get better by themselves; most things, in fact, are better in the morning.

Lewis Thomas MD

Top Study of 2015: *Psychiatric conditions cause physical diseases*

Association of Mental Disorders With Subsequent Chronic Physical Conditions. K. M. Scott et al, JAMA Psychiatry. Published online December 23, 2015. doi:10.1001/jamapsychiatry.2015.2688

An international study provides data for ending stigma

In searching for the most impactful paper of 2015, PL went to the most highly cited general psychiatry journal, JAMA Psychiatry (formerly Archives of General Psychiatry). There one finds a list of the most widely read articles, among which the top article listed was this one, which had just been published online 6 days before PL found it. In about a week, this paper had already been read more frequently than other papers on in JAMA Psychiatry from earlier in the year.

This high level of attention led PL to choose it as the top paper of the year, not because we think it is the best or the most creative or impactful for the long run, but because it has had an impact. Thus, PL wants to bring the paper to the attention of our readers.

This study was headed by many of the same researchers (like Ronald Kessler PhD) who ran classic epidemiological studies in psychiatry, such as the National Comorbidity Survey (NCS). In this study, researchers in 17 countries conducted epidemiological surveys of the frequencies of psychiatric conditions, using DSM-IV diagnoses, in 47,609 people, and they did so repeatedly 18 times over a decade (2001-2011).

They then asked the persons who were interviewed about whether they had been diagnosed with a list of medical illnesses, and at what age they had been so diagnosed or had first experienced symptoms. This analysis describes

the frequency of medical illnesses occurring AFTER onset of psychiatric diagnoses.

The key limitation to the study is that medical diagnoses are based completely on the self-report of patients, and were not independently verified or based on medical chart evidence. Another limitation, present with all such observational data, is that other confounding factors could exist and explain the association of mental and physical illnesses.

With those caveats in mind, using statistical regression modeling, the researchers found that mood conditions, anxiety conditions, and substance abuse each could explain about 3-13% of cases of a range of physical illnesses, such as cancer, diabetes, chronic lung disease, heart disease, and asthma.

When any psychiatric diagnosis was present, the risk of cancer was increased by an odds of 30% (odds ratio 1.3, 95% confidence intervals 1.1-1.5). The same was the case for diabetes. Heart disease risk was increased 70%, and chronic lung disease risk (presumably secondary to mediators like cigarette smoking) was doubled.

Many physicians focus on “physical” illnesses as if “mental” illnesses are unrelated. This report, within the constraints of its limitations as an observational study, reverses this discriminatory belief: If you want to control physical diseases better, diagnose and treat psychiatric conditions better.

Curbside Consults

Questions and cases from you

Question: I have not found lamotrigine to be helpful in treating hyperthymic or cyclothymic temperaments. What is your experience?

PL: This is a good question, and the discussion of affective temperaments for now can be found on the PL website. Future issues will discuss this topic in more detail. To put it briefly, readers are familiar with dysthymia, or mild depressive symptoms. But they likely are not familiar with the opposite state of mild manic symptoms, called hyperthymia. Cyclothymia represents the alternation between the two. In the classic German literature, especially in the work of Ernst Kretschmer in the early 20th century, these temperaments were seen as variants of manic-depressive illness (MDI). They were biologically and genetically related to that disease. They were not different conditions, as DSM sets it up, nor were they diseases in themselves. They were personality constructs, a constellation of traits seen in a certain way in persons with MDI, *in between their episodes*. These affective temperaments also were seen in relatives of persons with MDI.

With that basic definition, we can see the rationale for the PL approach to treating affective temperaments: the use of low doses of mood stabilizers. The treatment type is the same as in MDI, namely mood stabilizers, but since affective temperaments are the mildest shade of MDI,

then lower doses can be effective for them. There is some evidence to support this hypothesis in an observational study with divalproex in cyclothymia, and in some research with dysthymia, but so far there are no published treatment studies of hyperthymia.

Lamotrigine has been proven to be ineffective for acute mania. It does not work for manic symptoms directly. It also is less effective in prevention of manic than depressive episodes. Thus, of the four major mood stabilizers (lithium, divalproex, carbamazepine, and lamotrigine), the one agent that has a major weak spot, in the case of mostly manic presentations, is lamotrigine. If this is the case, then this agent is not likely to be effective for hyperthymic temperament, which is a purely manic condition. Nor is it likely to be as effective in cyclothymia, where manic symptoms are frequent, as opposed to the three other alternative mood stabilizers.

No studies yet exist on this topic, but your experience is consistent with the PL experience, and thus we don't recommend lamotrigine as the primary treatment for hyperthymic or cyclothymic temperaments. Instead low dose divalproex or lithium seem most effective for those conditions.

PL Reflection

Psychiatry is neurology without physical signs, and calls for diagnostic virtuosity of the highest order.

Henry George Miller MD 1970

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