THE PSYCHIATRY LETTER

Table of Contents

Questions, comments, cases? Write us at info@psychiatryletter.org

Savior treatments (ECT, Ketamine, VNS, etc):

Are they really better?

The prior summer double-issue of PL is followed here by a fall double-issue. The main topic in the special article is savior treatments, like ECT, vagus nerve stimulation (VNS), and most recently ketamine. These treatments, often devices as opposed to drugs, have been seen by clinicians as possible saviors for patients who fail to respond to standard medications, especially in severe refractory depression. The special article examines the claims for these treatments and finds them to have less benefit than often is claimed.

The Article of the Month reviews the maintenance efficacy of ECT and the claim that it is inherently better than pharmacotherapy. The History of Psychiatry section analyzes Freud's famous 1909 visit to Clark University in Massachusetts, the only time Freud ever gave an invited university lecture outside of Austria, and the only time he ever received an honorary degree from any university. The Psychopathology section discusses the theory and practice of four main approaches of psychiatry as explained by Leston Havens. The curbside consult questions address the validity of some DSM diagnostic cut-off rules and stigma issues around ECT.

We would like to remind readers that PL is nearing its final issues, which will end with the December 2018 issue. The PL website will remain open for questions and curbside consults, and will include commentary on new journal articles. E-books also will be made available there. In the meantime, PL readers also can buy a new psychopharmacology textbook authored by me, to be published by Oxford University Press in January 2019, now available for pre-order, as described in the sidebar.

Thank you for your continued support.

Nassir Ghaemi MD, Editor

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

Special Article: Savior Treatments in Psychiatry

ECT, TMS, VNS, Ketamine – Are they really better?

There have been a number of treatments in psychiatry that have been seen by clinicians and/or patients and the public as saviors, in one way or the other. These treatments have been seen as special, as better in some profound way than other treatments. Often these savior treatments have been devices, meaning non-drug interventions. Sometimes they have been drugs, but then they were usually not just pills, but rather intravenous injections or intranasal inhalants. Such interventions, superficially more profound than simply taking a pill, have been seen as more powerful than those pills. In this special article, PL will review a number of those savior treatments, beginning with historical antecedents (insulin coma, malaria therapy), and then the oldest in current use, electroconvulsive treatment (ECT), followed by transcranial magnetic stimulation (TMS), vagus nerves stimulation (VNS), and ending with the most recent claim to savior fame, ketamine and its derivatives.

Origins of ECT

ECT was introduced in psychiatry by Ugo Cerletti and Lucio Bini in Italy in 1938. They used electricity to produce convulsions, instead of drugs (camphor, metrazol), as had been introduced in Hungary by Ladislas von Meduna in 1934. Within two years of Cerletti and Bini's article on the topic, the first ECT demonstration was given at a 1940 APA meeting in the US. Competing with frontal lobotomy, also introduced in the 1930s, ECT became a central new treatment in psychiatry in the 1940s and 1950s. After the introduction of new antipsychotic and antidepressant drugs in the 1950s, frontal lobotomy use fell off, but ECT continued to be a prominent treatment.

Before ECT, there were two other new major treatments in psychiatry in the 1920s: insulin coma, and malaria therapy. It's worth discussing these treatments briefly, to provide historical context for the evolution of ECT, and for later recent claimants to the savior throne, such as VNS and ketamine.

Precursors to ECT: Insulin coma and malaria therapy

Contemporary readers may react with a certain recoil to names such as insulin coma and malaria therapy. But those interventions were not perceived in their age to be as harmful or illogically aggressive as they may seem today. It's worth appreciating this aspect of the matter as we later examine current claims to powerful treatment effects with new devices or interventions.

"...Before ECT, there were two other new major treatments in psychiatry in the 1920s: insulin coma, and malaria therapy"

Insulin coma

Insulin coma was introduced in 1927 by the Austrian psychiatrist Manfred Sakel. High doses of insulin, which had been newly discovered as a remarkable cure for diabetes, were given over weeks or months to induce states of severe hypoglycemia, nearing or inducing coma states. Glucose would be given after a brief coma to bring the patient back to consciousness. The danger was that coma could lead to death if

hypoglycemia was too severe or rapid. The benefit was that patients often improved. These patients often had schizophrenia, or some kind of severe chronic psychotic state.

Did insulin coma work? If so, why did it work? Highly qualified and well-trained psychiatrists and researchers observed that insulin coma seemed to help psychotic symptoms. But it is hard to know whether this was the case in reality, as no control groups were used to correct for natural history of symptom improvement. If there was real benefit with insulin coma, one possible mechanism was the induction of seizures in some patients, which might help in the same way that ECT did later.

Insulin coma was used in the US prominently in the 1930s through the 1950s. It was used occasionally in Europe even into the 1980s in some hospitals.

Malaria therapy

In 1917, malaria therapy was introduced by the chairman of the department of psychiatry in the University of Vienna, Dr. Julius von Wagner-Jauregg. Blood from malaria patients was injected into other patients with chronic psychosis, often diagnosed with schizophrenia, sometimes with general paralysis of the insane (GPI, later found to be neurosyphilis). It was observed that psychotic patients would develop malarial fevers, and then their psychosis would improve. This treatment was revolutionary because he showed for the first time that a psychotic state could resolve completely with a biological intervention. This fact proved that at least some psychiatric conditions were biological diseases, that could be cured with physical interventions, as opposed to purely psychologically caused. As a result of this impact, von Wagner-Jauregg was the first psychiatrist to receive the Nobel Prize in 1927. (The only other psychiatric treatment to receive a Nobel Prize was frontal lobotomy, given to its inventor Egas Moniz, in 1949).

"...[Malaria therapy] proved that at least some psychiatric conditions were biological diseases, that could be cured with physical interventions, as opposed to purely psychologically caused..."

Did malaria therapy work? If so, why? There is reasonable evidence that malaria therapy in fact worked for many psychotic patients, although again the absence of a control group means that we cannot know how much patients might have improved. There is more reason to think that malaria therapy worked than other treatments in that era partly because the effects were more rapid than in other cases.

If it worked, its mechanism likely involved the fact that many cases of psychosis in the early 20th century involved GPI. Neurosyphilis was indistinguishable in many of its phases from mania, depression, or schizophrenia. The spirochete is sensitive to heat. When malarial fever occurred, the heat would kill spirochetes in the brain, and the syphilitic disease would stop. This process of killing the bacteria that cause syphilis was handled much more effectively with the introduction of penicillin into practice in the 1940s. By the 1950s, GPI was wiped out, the largest cure in psychiatric practice. Penicillin can be seen as the most effective psychiatric treatment ever.

But before penicillin, malaria therapy had shown the way. It proved too harmful by itself to be a long-term cure, though, since, as one critic remarked, it cured one disease by causing another.

Back to ECT

Despite the introduction of antidepressants and antipsychotics, ECT remained in common use for refractory depression especially since the 1960s

onward. In some countries, its use is limited by law, but in most countries, most clinicians support its use. An alternative was developed 1985, transcranial magnetic stimulation (TMS), which provides magnetic activation of neurons across the skull. TMS was used in neurology for various conditions and introduced for the treatment of depression in the 1990s.

The use of ECT and TMS is relatively common for acute exacerbations of psychopathology. ECT in particular is proven effective for acute mood states, especially depression but also mania. The efficacy of ECT is most proven for severe depression, especially of melancholic and psychotic subtypes. Such benefit is present in both bipolar and unipolar depressive illness. ECT is also used most commonly in hospital settings, and for older persons who may not be able to tolerate polypharmacy with psychotropic medications. In the United States, because of insurance restrictions, ECT is used in hospitals very frequently, as it is reimbursed without much trouble. Many clinicians believe that ECT is more effective than medications in general, including short- and long-term treatment. However this is not the case. ECT may be more effective than antidepressant medications for severe acute depression, in terms of overall efficacy or in terms of more rapid response. The enhanced rapidity of ECT response may be useful especially to reduce acute suicidality and to speed discharge from the hospital. However, the concept that ECT is more effective than most or all psychotropic medications in general is not true. Outside of the acute phase, in long-term maintenance treatment, one frequently sees that ECT is used on a monthly or more frequent basis for months or years of treatment, after patients fail antidepressant medications in particular. In the longest randomized one-year maintenance trial of ECT versus medications for treatment of refractory unipolar depression, though, ECT was not more effective than medications in maintenance treatment. In other words, ECT did not prevent mood episodes more effectively than medications, even in patients who had been selected to fail antidepressant agents. It is worth noting that in that study, the medications given for the maintenance phase were lithium plus nortriptyline, while most of the medications failed before entry into the study were serotonin reuptake inhibitors (SRIs). Thus, the similar efficacy of lithium plus nortriptyline to ECT may reflect the special maintenance effectiveness of those agents, lithium in particular, as opposed to serotonin reuptake inhibitors. Thus, it may be more accurate to say that ECT is not better than lithium and perhaps tricyclic antidepressants for long-term maintenance treatment of unipolar depression, but it is possible that ECT is more effective than SRIs.

"...ECT is not better than lithium and perhaps tricyclic antidepressants for long-term maintenance treatment..."

It also is worth noting that the observed efficacy of ECT may not be entirely due to its biological effects. Randomized trials of ECT which compared to sham ECT, where anesthesia is given but no seizure is obtained, find notable benefit with sham ECT. In these studies, ECT often is better than sham ECT, which supports its efficacy, but it is important to note that sham ECT also has benefit, and thus some of the benefits seen in ECT may be due to placebo-like effects of receiving this intervention.

The mechanism of ECT

The mechanism of action of ECT involves the induction of seizure, which is thought to reduce

depressive symptomatology. It has been observed in the past that patients who have epilepsy can experience forced normalization, which is the observation that depressive states are more common when seizures are under control, and less common when seizures are more active. The idea then followed that depression could be treated by causing seizures. The exact mechanism by which seizure induction leads to depression improvement is unknown. There has been some work suggesting some changes in neuronal markers, such as BDNF, after ECT. But whether these changes are specific or nonspecific to ECT is unknown. Cognitive side effects are known to be associated with ECT, and they seem to be worse with long-term treatment and in those who do not experience antidepressant benefit with ECT. In those for whom ECT is effective for their depressive symptoms, cognition tends to improve.

TMS

TMS or transcranial magnetic stimulation is not as effective as ECT. It has been proven in treatment of Parkinson's disease and other neurological syndromes, and is shown to be effective for the acute depressive episode. However, unlike ECT, it has not been shown to be effective in treating refractory depression, and thus is not shown to be more effective than standard antidepressant psychotropic medications. TMS has much fewer side effects in ECT, but it also is less effective. Again, like ECT, it has not been shown to be effective or even studies outside the acute phase of treatment of depression long-term maintenance treatment is not been shown to be effective, and should not be assumed to be effective long-term.

Vagus Nerve Stimulation (VNS)

VNS was developed, like TMS, for neurological diseases and then expanded to depression. Since VNS is a device, FDA regulations regarding it are different than for drugs. In general, FDA thresholds for approval of devices are lower than for drugs; in other words, it is easier to get a device onto the US market than drugs. In fact, in the case of VNS for treatment-resistant depression, the device was allowed onto the market without any randomized clinical trials (RCTs), unlike drugs. VNS entered the US market in 2006 based on observational studies showing benefit in persons with past nonresponse to antidepressants, a definition which, as shown below in the ketamine section, is not a valid manner of demonstrating treatment resistance.

"[VNS] was allowed onto the market without any randomized clinical trials (RCTs), unlike drugs..."

Without randomized data, confounding bias makes it impossible to accept observational data as proof of efficacy. Last year, in 2017, many newsletters simplistically accepted the observational results of a 5-year database that the FDA had organized. In that database, there was a higher 5-year remission rate in the VNS plus treatment as usual group versus treatment as usual (without VNS; 43% vs 26% respectively). Those results are not true necessarily, though, and can reflect other outcome factors. For instance, those treated with VNS might have received more visits and more attention than those who did not. They might have been less ill by natural history. The placebo effect of VNS was not controlled at all; those who received it might have expected to improve more than those who never received it. In short, there are many confounding factors that could cause differences between the groups.

In sum, VNS still is not proven effective in a randomized trial versus a sham control. It involves surgery and a large neck scar, thus it is not benign. Given the lack of randomized proof of efficacy, and real risks, as well as expense, many clinicians and payers have not supported VNS, and PL shares their view.

Ketamine

An alternative to both ECT and TMS could be ketamine, given intravenously, or esketamine, given intranasally, which again would be effective for the acute depressive episode. Again, as with ECT, there is no proof of benefit outside of the acute phase. Therefore, maintenance efficacy with long-term treatment cannot be assumed, it has not been proven. There may be a benefit to ketamine for more rapid response in acute depressive symptoms and for more rapid reduction of suicidality, but again this short-term immediate benefit does not translate into a long-term prevention of future symptoms. Unipolar depressive illness is a long-term recurrent disease, in which many mood episodes happened in a lifetime. All of these medications-ECT, TMS, and ketamine- are at best short-term treatments, for acute mood symptoms, and do not have any proven benefits for the long-term illness. This does not mean they are useless, but it also means that they are not profound solutions to the overall disease. Their use is much like steroids in autoimmune diseases, where benefits are present and even crucial for acute exacerbations, where steroids may be lifesaving. Long-term treatment, though, does not treat the underlying cause of the autoimmune disease. Steroids also have more side effects when given long-term, without any proven benefit. The same would be the case with ECT and ketamine and TMS for recurrent unipolar depressive illness. These medications may have acute short-term benefits that may even be lifesaving, but they do not treat the overall disease, and may have no long-term benefits. They do have many side effects though which would increase long-term.

"... [Most of the ketamine literature] is based on a definition of treatment resistance that is solely dependent on past recall of prior antidepressant treatment trials. This past recall is not accurate..."

Invalidity of defining treatment resistance

Another factor that is important with the ketamine literature is that most of it is similar to the VNS literature, in that it is either purely observational, and not randomized, or it is based on a definition of treatment resistance that is solely dependent on past recall of prior antidepressant treatment trials. This past recall is not accurate, it seems. The evidence for the invalidity of this past recall can be found in studies of other treatments that have received FDA indications for treatment-resistant depression, such as dopamine blockers like aripiprazole or quetiapine. Those agents had to conduct studies based on an FDA requirement of failing a prospective trial of a standard SRI agent. In those studies, patients were initially selected as having failed at least two or more prior antidepressant trials. Then they were treated with an SRI prospectively for 8 weeks, and had to fail that trial before entering the pivotal phase III randomized trial for FDA indication. Surprisingly, about 60% of patients with a history of multiple failed antidepressant trials actually responded to a simple open-label trial with a different SRI. This 60% response rate is similar to what is reported in non-refractory depression studies. In other words,

reported failure to respond to past antidepressant trials was not confirmed in a prospective trial as a valid way of defining treatment resistance.

In studies of ketamine, the vast majority are based on this invalid method of relying on past failed antidepressant trials. Then a ketamine trial is effective and it is claimed that ketamine is more effective than those other antidepressants. The only way to make this claim validly would be to follow the FDA paradigm of failing a prospective trial of an SRI. Ketamine itself has not been tested in this manner, but recently its enantiomer esketamine has been tested in this manner in the process of its development for FDA indication by its manufacturer.

"PL does not recommend ECT or TMS or ketamine for long-term treatment of any depressive illness..."

As context, in the antidepressant literature, with over 500 RCTs, it has been found that the overall benefit seen with antidepressants is about 2-3 points greater than placebo on standard depression rating scales (such as the Hamilton Depression Rating Scale, HDRS, or the Montgomery Asbserg Depression Rating Scale, MADRS). In the randomized studies which define treatment resistance retrospectively based on reported failure of past antidepressant trials, it was reported that ketamine produced a benefit over placebo of 5-10 points, which is larger than the 2-3 point difference seen with standard antidepressants. However, in a recent esketamine trial for FDA registration with a failure of prospective antidepressant treatment required, it was found that esketamine was better than placebo by about 3 points on the MADRS. This effect size of benefit is similar to what has been found with standard SRIs. Thus, this result would suggest that this derivative of ketamine may be effective for depression, but not more effective than standard SRI antidepressants.

Thus PL does not recommend ECT or TMS or ketamine for long-term treatment of any depressive illness, but PL would be open to their use for short-term acute mood episodes for which medication treatment is either unresponsive, unavailable, or intolerable. Based on the best available research literature, PL is not convinced that ketamine or its derivatives are more effective for depression, though, than other standard monoamine agonists.

The PL Bottom Line

- There are no savior treatments that work long-term in psychiatry.
- ECT is the most effective treatment among those reviewed, but it is effective acutely, not long-term.
- TMS is not more effective than standard antidepressants.
- VNS has not been proven effective with the same rigor as antidepressant drugs (i.e., with randomized data).
- Ketamine and its derivatives have not been proven more effective than standard antidepressants. Any benefit again is acute, not long-term.

Current Study of the Month: *Maintenance efficacy of ECT*

Electroconvulsive therapy in the continuation and maintenance treatment of depression: Systematic review and meta-analyses A. Elias et al, Australia and New Zealand Journal of Psychiatry. 2018;Vol. 52(5) 415–424

Limited proof of benefit, and clearly not better than lithium

This systematic review is a good summary of decades of RCT research on efficacy of ECT for the long-term, in maintenance prevention of depressive episodes. This outcome gets at the claim that ECT is better than other treatments in some inherent way. There is a difference between acute symptomatic improvement, as opposed to long-term disease modification. ECT provides acute symptomatic improvement, as described in the Special Article. But the question of whether it is better than other drugs inherently implies disease modification, something more than mere current symptom improvement. For that claim, one has to show long-term benefit, which means maintenance prevention trials.

As described above in relation to VNS, any claim to benefit for any treatment needs to be made with a RCT so that confounding bias can be controlled. The first observation to make in this review is that there only are five RCTs of ECT for maintenance efficacy. Seven observational studies have been published but they were not randomized. The five RCTs studied overall 436 patients with three studies having only 6-month outcomes. One study had a follow up of one year, and another study two years. In general, the maintenance phase of unipolar depressive illness is defined as beginning at one year. Thus, there only are two studies that are one to two years in duration for long-term ECT efficacy. Given the common use of ECT long-term in many patients, it is important to realize this fact, that only two studies, with 89 patients overall, actually examine such long-term use. In other words, all this long-term treatment in practice is based on data on 89 patients.

Because there are so few studies, this meta-analysis mainly focused on the 6-month outcomes, so as to include all five studies. PL readers should keep in mind that these 6-month outcomes do not reflect the maintenance phase, but rather the continuation phase after acute improvement. In other words, initially patients were treated with ECT. If they responded, they were randomized to continue with ECT, or to switch back to medication use alone.

PL readers should realize that this is the classic "enriched" design, which PL has shown to be invalid (see PL website). In that design, only acute treatment responders are included in the study to assess further treatment response. This is a selection bias that massively supports apparent "response" for the drug which is selected to be included. So it is not surprising that ECT would be effective versus comparisons if only ECT responders are included in the study. This enriched selection bias is a problem especially around the acute episode. If ECT helps depression for 2 months, and then you stop it, and the patient relapses 2 weeks later, this is not maintenance prevention of new episodes, but rather the same acute episode continuing to happen. In fact, it is the case that the average unipolar depressive episode lasts 6-12 months untreated, and this is why the maintenance phase

is not viewed as beginning until after this 6-12 month period. Any relapse before that time is the same acute phase continuing, not a new episode.

Of these five studies, only one compared ECT alone versus pharmacotherapy alone (which was lithium plus nortriptyline). That study was the one that found absolutely no benefit with ECT. Both treatment options were the same. Even though that study preselected for ECT responders, it appears that lithium plus nortriptyline is so effective that these medications were just as good as ECT, even in a sample that was preselected to reflect ECT responders.

The longest study, which was a two-year trial ,compared ECT plus nortriptyline versus nortriptyline alone, and found notable benefit with ECT.

Given these two studies, it appears that nortriptyline may not be the effective comparator agent to ECT, but rather lithium might have shown marked efficacy in the largest trial, to such an extent that ECT benefit in maintenance treatment was not seen.

The PL view is that this high drug response likely was driven by lithium, which, unlike nortriptyline, has extensive evidence of benefit for prevention of depressive episodes in unipolar depression (as well as bipolar illness).

Clinical implications

How should PL readers interpret this study's results in terms of how it applies to their clinical practice? The simplistic interpretation would be that the meta-analysis supports maintenance efficacy with ECT. But this conclusion, which is made by the authors, ignores the fact that the 6-month outcome is not the maintenance phase, and that this conclusion requires not including the largest negative trial. Further, comparing the details of the various trials, it appears that ECT may be more effective than standard antidepressants for maintenance treatment of unipolar depression, but it is not more effective than lithium. Hence, these data could be interpreted as supporting using lithium for maintenance treatment of unipolar depression after acute treatment with ECT. Interestingly, in the 1970s-80s, before the SRIs were developed and came into common use in the 1990s, some clinicians practiced this way: ECT for acute depression, and lithium for prevention. The ECT maintenance RCT literature would seem to support this practice.

The PL Bottom Line

- Maintenance efficacy of ECT for prevention of new depressive episodes is based on a few studies, mostly of 6 months duration.
- Longer studies suggest ECT benefit over standard antidepressants, but not over lithium.
- Clinical practice that is supported with these data would be acute treatment of depression with ECT, followed by long-term prevention of depression with lithium.

History of Psychiatry

The discovery of modern antidepressants

PL Note: The story of the discovery of the first modern antidepressant, imipramine, involves a prominent existential-psychoanalytic psychiatrist, Roland Kuhn, who found that a new class of drugs did what the best psychotherapy could not. The psychiatric historian Edward Shorter describes this process well. What is not described here is that Kuhn also found that imipramine was most effective for his patients with melancholic (or "endogenous" depression, but not for those with non-melancholic (or "exogenous") depression. Kuhn and others used the phrase endogenous and exogenous as synonyms for melancholic and non-melancholic depression, though this is not the case. For our purposes, it's important to note that from the start, monoamine agonists were not effective for all kinds of depression, but only some kinds, specifically for TCAs, they were less effective in non-melancholic depression.

From: Edward Shorter, A History of Psychiatry, New York, John Wiley and Sons, 1997, pp 258-261

In 1950, the J. R. Geigy pharmaceutical firm in Basel asked staff physicians in the Munsterlingen asylum in Switzerland to see if an antihistamine that Geigy had developed might serve as a sleeping pill....One of these staffers was Roland Kuhn, then 38, a tall, distinguished, and cultivated psychiatrist who combined an exceptional grasp of the humanities with a background in biochemistry.....He was...an adept of psychoanalysis...and was a good friend of Ludwig Binswanger [a friend and follower of Freud, and a central founder of existential psychotherapy]...

Then Kuhn had one of those road-to-Damascus-type experiences. He had been treating with psychoanalysis a young woman whose complaints seemed to be of a "neurotic-hysterical" nature. He made great progress with psychodynamic therapy, "bringing out unconscious material that corresponded exactly to Freud's theories. Everything went beautifully and she was cured. A few days later she came to my office again, garishly made-up and perfumed, with costume jewelry hanging all over her, dressed in loud colors...and demonstrating irritable and euphoric mood changes, pressured speech and flight of ideas." Kuhn then realized he had made a mistake. The correct diagnosis was mania. He had falsely ascribed a spontaneous recovery to his psychoanalytic "cure." As so often happened in those days, Kuhn had also missed her earlier depression given her a misdiagnosis of "hysteria." For Kuhn, manic-depressive illness was an organic condition having little to do with Freud's ideas.

Yet as Kuhn fell away from psychoanalysis, he asked himself, what can we do to help patients like this? Admitting her to the mental hospital for ECT seemed a bit much. "How often I said to myself, 'We should improve the opium cure!' But how?"

"He had falsely ascribed a spontaneous recovery to his psychoanalytic 'cure.'"

Then in 1952, the discovery of chlorpromazine became known. Kuhn and his colleagues put depression and mania at the back of their minds for the moment. The Munsterlingen staff received free samples of chlorpromazine from Rhone-Poulenc for trials on their schizophrenic patients....Kuhn asked Geigy... if the hospital might try another drug in antihistamine series, one with a chemical side chain exactly identical to chlorpromazine's.... The staff tried it on patients with schizophrenia. It makes many of them worse, converting quiet chronic patients into agitated whirlwinds of energy. Kuhn consulted with Geigy scientists on

what the drug could possibly be doing to procure such bizarre effects, and sometime in 1955 the decision was made to give it to some depressed patients. The response was "absolutely incredible, so exciting"....Kuhn and the Geigy people had obviously discovered a drug that could relieve depression.

In the first 40 depressed patients who received it, some of the recoveries were dramatic....The patients themselves spoke of a "miracle cure"...

In the spring of 1958 Geigy named the compound imipramine (Tofranil). Imipramine was the first of the "tricyclic" antidepressant...rival tricyclics flooded the market, the Merck Company, for example, bring out amitryptiline (Elavil) in 1961. By 1980 American physicians were writing 10 million prescriptions a year for antidepressants alone, the great majority of them tricyclics.....

PL Reflection

I like the dreams of the future better than the history of the past.

Thomas Jefferson
Letter to John Adams

Psychopathology

The four schools of psychiatry

PL Note: The psychiatrist Leston Havens explains here the four main approaches to psychiatry, which he described repeatedly in his work. They are the interpersonal, psychoanalytic, existential, and objective/descriptive schools. Here he summarizes their theory and practice.

From Leston Havens, Participant Observation: The psychotherapy schools in action, 1983, Northville NJ: Jason Aronson, pp 151-154

[There are]...four principles sharply separable from those underlying the best-known ways of doing psychiatric and psychologic work....

First, interpersonal work is directed at the 'other people' in the room, what I have called the social unconscious permeating human transactions. Until the medium of communications is cleansed of its distorting images, it is assumed that no reliable exchanges can take place.

Psychoanalysis, in contrast, incubates the distorting images. These in their fully developed form, the transference neurosis, constitute the lesion to be treated. The partly detached, neutral presence of the analyst invites the transference neurosis which, it is assumed, can then be dealt with interpretively.

Existential workers, in further contrast, neither offer themselves as screens, like analysts, nor attempt to move the distortions away to be examined elsewhere. By being where the patients are, they assume they offer no target for transference. Inside the patient, as it were, they look out at the patient's world.

In medical psychology, finally, and some psychoanalysis, doctor and patient form a cooperative alliance to examine and deal with the distortions. This point of view takes for granted that doctor and patient can be objective, that there is some part of the mental life of both doctor and patient untouched by the distorting introjects.

Second, interpersonal work assumes that the other people in the room make the patient anxious and can only be removed by indirect means. These means I have called playing the transferences. The principal device is talking about the introjects....

Psychoanalysis, in contrast, requires that the patient bear considerable anxiety. To reduce it prematurely would be to abort transference development. With transference development come the patient's characteristic ego processes, which are to be analyzed too.

In existential work anxiety is shared with the therapist. Existential therapists, being with their patients, help bear the anxiety, as well as other feelings....

In medical psychology (what I have called elsewhere objective-descriptive psychiatry), anxiety is reduced by medication and reassurance. In behavior therapy, it may be reduced by gradual exposures to what is frightening....

Third, according to interpersonal theory, the presence of the other people in the room and the anxious responses to them have been learned. Introjects have rubbed off, as it were, from reality; the patient's projections are assumed to reflect the patient's experiences. People, in short, drive each other mad.

Psychoanalysis, in contrast, assumes the prince of instincts in conflict with each other or with psychic structures. The results of these conflicts are projected. These projects are fantasies that may reflect more of wishes and their counterforce than they do of the patient's actual experience. As a result, psychoanalysts are in danger of seeing everything as fantasy just as interpersonalists fall victim to blaming everything on reality.

Existentialists, in turn, are less likely to judge either the patient or the world. The two are to be helped bear one another. Therefore existentialists are in danger of accepting what needs to be changed.

The medical psychologists, in turn, when they are biologists, locate the lesions in the body and attempt to correct that. When they are educators, hypnotists, or behaviorists, they work on the mind. They fall victim to authoritarian manipulation and coercion.

"... psychoanalysts are in danger of seeing everything as fantasy just as interpersonalists fall victim to blaming everything on reality...."

Fourth, as long as the patient lives with the old anxiety-provoking projections, his or her behavior must remain the same. As soon as the medium between the patient and other is cleared and the past reconstructed, the behavior can change. Interpersonalists assume that in the absence of continued reinforcement old patterns will change.

Psychoanalysts, in contrast, regard social misperceptions as a product of internal conflict. Until the conflicts are resolved and the resulting fantasies dissipated, behavior cannot change. Psychoanalysts assume that surfacing and interpreting the fantasies, conflicting forces, and accompanying behavior will change them all.

Existential psychiatrists do not want to change the patients. Expressing unconditional positive regard and being with one another, therapists and patients may or may not change.

Finally, medical psychologists diagnose and treat. The behaviorists among them do not speak of perception and behavior, but of stimulus and response. They assume that changing the stimulus received need not change the response; the response itself must be altered.

Thus the great schools direct themselves at different targets: what occurs between people, what occurs within individuals, or the body and its behavior. Without seeing clearly how it can be built, one imagines a psychiatry ready to do battle on all or any of these fronts.

PL Reflection

Don't look for yourself outside yourself

Ralph Waldo Emerson

Curbside Consults

Questions and cases from you

Question: The background to my question is the following: I take particular interest in synthetic/designer drugs. With the advent of the internet, it has been very easy for people to import drugs, synthetic cannabinoids, synthetic cathinones, "research chemicals" such as "2C" and an astounding variety of other chemicals. Traditional testing usually does not reveal much: urine testing is usually limited to our traditional "NIDA-5" (cocaine, amphetamines, marijuana, opiates/opioids, PCP etc.) or a few additional chemicals.

My main question follows: We are now seeing people who consume a large quantity of these synthetic substances and remain psychotic or symptomatic for a long period of time. The DSM cut off of 1 month is clearly not enough as their symptoms don't remit for several months. What is the implication of this course for their diagnosis? Is this condition still just a substance-induced psychotic or mood disorder or something more? Could some substances cause some sort of permanent change in the brain that causes a fixed mental disorder?

PL: The DSM cut-off of 1 month has no scientific basis. It is, like most DSM criteria, a social construction based on the profession's social preferences at a given moment. 20 years ago the cut-off was 6 months. A prominent substance abuse expert once described searching for the scientific source for the 6-month cut-off. He went from scientific paper to scientific paper, each referencing another paper, until he finally ended up with a primary source reference in a textbook. He then went to the textbook and found that the 6-month cut-off was stated without any further

citation. In other words, there were many sources which ultimately lead to nothing.

This is the case with many such rules of thumb in psychiatry, which may have some pragmatic value, but are not based on some solid ground of scientific fact.

The 6-month cut-off was later changed in DSM to 1 month, mainly because of clinical opinion and concern that 6 months was "too long." Too long based on what? There was no scientific ground for the original 6-month criterion, nor was there any for the one-month criterion. It was just felt clinically by many practitioners that 6 months was too long. That meant that you had to wait 6 months until someone stopped drinking or using drugs before you officially diagnosed them with "MDD" or "GAD" and then prescribed monoamine agonists. In fact, clinicians can prescribe medications whenever they want, without making a specific diagnosis. The making of a diagnosis need not lead to prescribing a medication, nor does it justify the latter. In medicine, we often make diagnoses without prescribing treatments. We often prescribe without making diagnoses. It should be the same in psychiatry.

But because of the DSM ideology and the attempt by the American psychiatric leadership to tie DSM to treatment, this medical approach has been replaced by an overly obsessive focus on using DSM criteria to justify treatment.

This ideological mistake plays out clearly with the question of substance abuse. There's no scientific evidence that one month is a factual cut-off for any diagnosis related to substance abuse. Some substances cause clinical symptoms over minutes; others over hours; others over days; others over weeks; others over months; some might last years. One month is not a general scientifically meaningful cut-off for anything. It's just another pragmatic DSM claim, meant to put all of psychiatric practice into a single straight-jacket.

Here are some examples that disprove the one-month generic cut-off:

There is plenty of research, including in neuropathology, which shows that chronic alcoholism is associated with permanent changes in the brain. Cerebellar vermis degeneration is now well-known. Lesions in other parts of the brain are associated with Wernicke-Korsakoff psychosis, which involves chronic delusions lasting years. Further, chronic auditory hallucinations lasting years were associated with some forms of severe alcoholism.

So these conditions involve substance abuse with permanent changes lasting years.

Shall we use the phrase "substance-induced psychotic disorder" for Wernicke-Korsakoff syndrome and chronic alcoholic hallucinosis? We can do so if we want to be bureaucratic. Or we can just use the scientifically-based clinical diagnoses given above.

Another example is steroid-induced mania. Intravenous steroids can cause manic episodes, even in persons without spontaneous manic episodes (i.e., without bipolar illness). Once induced, such manic episodes can last weeks to months. There is no one-month cut-off.

So, in short, we know already that substance abuse, with well-known classic substances such as alcohol and steroids, can produce mood and psychotic states that easily last longer than one month. Further, it was the case in the past that 6 months was viewed as a cut-off before ascribing psychotic and mood symptoms to substance abuse alone. There is no reason one should be we to the

one-month cut-off as having any scientific meaning.

It may be that these new designer substances may have longer lasting influences on the brain and thus cause longer clinical symptoms. This effect would not be surprising or unusual, as it is also the case with older traditional substances, such as alcohol and steroids.

Question: How do you convince reluctant patients to accept ECT?

PL: Many patients have a negative opinion about ECT in the United States, and in other countries, partly based on misinformation, and partly based on stigma. Misinformation can involve just the general principle of receiving a treatment that involves causing a seizure. The question could be whether it is reasonable to cause a seizure in the brain as part of a treatment for a psychiatric state. It would seem to be an extreme and excessive approach. There is some rationale to this concern. One has to admit that the concept of using seizures to treat depression or psychosis is speculative, based on an older epilepsy literature. Its biological mechanisms are not well known or worked out in detail. While accepting those limitations, it's also important to explain to patients that there is good clinical literature that supports the short-term acute efficacy of ECT, with multiple randomized trials showing benefit over sham ECT.

Perhaps the most important point to discuss regarding information about ECT is the risk of cognitive harm. Too often this potential harm is discussed in an all-or-nothing manner. Critics will say that ECT harms memory, period. Defenders will say that ECT does not affect memory, period. Neither are correct. ECT can worsen memory, by causing cognitive side effects, in some people. Usually, this cognitive harm seems to occur as a short-term side effect, without long-term impact. In some people, though, there appears to be long-term cognitive harm. This should not be very surprising, as patients given ECT have long-term cognitive impairment anyway as part of their mood or psychotic illnesses. We know very well that manic-depressive illness, for instance, is associated with cognitive impairment, not only during mood episodes, but even permanently in periods of remission. The risk of dementia is increased 2-4 fold in such persons. Thus, they are predisposed to cognitive impairment, and anything which can worsen cognition, such as ECT, can lead to further cognitive impairment in such conditions.

It could be that the persons who experience the most cognitive impairment with ECT are those who do not improve with treatment. Their mood condition continues, and it worsens cognition, along with the direct effects of ECT.

In contrast, most persons who improve for their psychiatric condition with ECT do not experience cognitive impairment, at least in the long run.

Thus, the issue of potential cognitive impairment should be discussed in the context of the risk of cognitive harm from the mood illness itself, as well as whether or not someone improves with ECT.

In relation to stigma, rather than simple misinformation, the problem can be deeper. Some patients in the US have been influenced greatly by anti-psychiatry movies, such as Ken Kesey's "One flew over the cuckoo's nest." As with much that comes out about psychiatry in the media, that movie was ideologically one-sided, and it had a very harmful impact on the population. One can try to counteract such false beliefs with a patient if the patient has a good relationship with the clinician. But in the absence of such a

relationship, the cultural opinions of a patient will be difficult to change. In some countries, such as Italy, there has been long cultural debate about ECT with many critics of ECT and psychiatry having influence on public opinion. In such settings, a single clinician can do little to counteract generations of opinion formed by critics of ECT and psychiatry.

Question: I have the impression that SRI's often seem to work better for anxiety than depression, but that may be a reflection of depressive syndromes not necessarily being MDD. I'm not sure this is statistically answerable, but do you know how the effect size for SRI treatment response for unipolar MDD compares with the effect size for SRI treatment for anxiety disorders such as GAD or panic disorder?

PL: PL fully agrees clinically that SRIs are better for anxiety than depressive symptoms. The effect size for "MDD" for difference between SRI and placebo is about 0.30 on Cohen's d (which is small and below the typical clinically meaningful effect threshold of 0.5). The effect size for "GAD" is a good question that has not been discussed in PL previously. In a review of a recent meta-analysis (B Bandelow et al, Int Clin Psychopharmacol, 2015, 30:183-192), PL found that the difference between most SRIs and placebo was about 0.5.

So the effect size of SRIs for MDD is 0.3, which is small; and the effect size of SRIs for "GAD" is 0.5, which is moderate. This research literature thus supports clinical impression: SRIs are more effective for anxiety than for depressive symptoms. This is another reason why the term "antidepressant" is not accurate. If anything, these agents should be called anxiolytics. In fact, they are monoamine agonists, and they have some clinical benefit for anxiety and depressive symptoms, more so for the former than the latter.

PL Reflection

God is asleep, not dead.

Rilke

The Psychiatry Letter, P. O. Box 400536, Cambridge MA 02140. Editor and Founder: Nassir Ghaemi MD. Managing Editor: Alcides Albuquerque MD. The Editorial Board can be found on www.psychiatryletter.org. A monthly independent newsletter not owned, operated, or affiliated with any organization. It receives no financial support from any source other than subscribers. Disclosures: Dr. Ghaemi is employed by Novartis Institutes for Biomedical Research. In the past 12 months, no relationships with the pharmaceutical industry exist for any other members of the PL Editorial Board. Disclaimer: The medical information provided in this newsletter is information based on general scientific knowledge and/or clinical experience. It is not specific advice intended for individual treatment of a specific patient as would be provided in an in-person professional consultation. If users need specific medical advice for specific treatment decisions, they should consult an appropriate medical professional. No warranties are given in relation to the medical information supplied. No liability will accrue to the