The Psychiatry Letter

The oxcarbazepine myth

In this issue we discuss the use of a novel anticonvulsant, oxcarbazepine (Trileptal), which is increasingly popular as a purported mood stabilizer. This popularity is based on the assumption that it must be similar to carbamazepine in its efficacy, since it’s similar to carbamazepine in its chemical structure. We discuss the general principle that structural similarity of drugs doesn’t translate to clinical similarity of efficacy.

The drug of the month is trazodone, which is the only medication used for sleep which improves sleep cycles.

The case of the month examines a messy case where many drugs are used for unclear purposes for an unclear diagnosis. Such clinical scenarios are not uncommon, and PL discusses the concept of a “working diagnosis” that is testable, and thus can be confirmed or refuted, as a potential solution.

The topics of bupropion for bipolar depression, and the use of the TEMPS scale for affective temperaments, are addressed in Curbside Consults.

As with all issues this year, continuing medical education (CME) and continuing education unit (CEU) credits are available for the special article through the PL website.

We appreciate your continued support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley
CME Special Article: The oxcarbazepine myth

Overusing drugs like oxcarbazepine (Trileptal) and gabapentin and what to do about it

About two decades ago, a new class of anticonvulsants emerged, with clearly less side effects than prior agents. Today they are increasingly used. In addition to a Drug of the Month review of oxcarbazepine in PL May 2015 issue, this issue focuses again on that agent as a special article. This agent is used increasingly, and there is reason to examine in more detail whether this usage is justified.

The chemical analogy

The standard viewpoint these days, taught routinely, is that oxcarbazepine is just as effective as its chemical cousin carbamazepine, but it has much fewer side effects, and is thus preferable. Thus, one routinely sees that patients are given oxcarbazepine, and usually not given carbamazepine. Further they never have been treated with more effective mood-stabilizing agents like lithium, valproate or even lamotrigine.

Let’s begin with the chemical structure comparison. Most clinicians haven’t seen those structures, and instead assume they’re similar. It’s worthwhile visualizing the claim, shown in the figures below.

First, there’s carbamazepine:

You’ll note the classic tricyclic structure. It shares that structure with tricyclic antidepressants and with phenothiazines. We’ll come back to this point.

Now let’s turn to oxcarbazepine:

You’ll notice the difference: a double bond oxygen side chain. That’s it.

How much does an oxygen double-bond matter?

Before we answer that question, let’s go back to the question of that tricyclic structure. How much does the tricyclic structure matter?

Let’s look at two different tricyclic medications. First, imipramine, a tricyclic antidepressant:
Now let’s look at chlorpromazine (Thorazine), the first classic phenothiazine antipsychotic:

And an oxygen double bond produces one drug which causes mania (imipramine), and one drug which treats mania (carbamazepine): Completely opposite clinical results.

What’s the difference between oxcarbazepine and carbamazepine?

An oxygen double-bond!

Would you say that we should give imipramine to treat mania, since it only differs from carbamazepine by an oxygen double bond?

If not, then why do people say that we should use oxcarbazepine for bipolar illness, when it differs from carbamazepine in a similar way?

In short, there’s no scientific chemical logic to the above claim.

Now let’s turn from biological speculation to clinical data, which is more important scientific evidence.

Clinical data

Oxcarbazepine was used and studied in the 1980s in Europe, and there are two small double-blind studies comparing it to haloperidol in acute mania. In those studies, both agents improved. But there was no placebo control. Since mania improves spontaneously, and rather quickly, it isn’t clear that such data would support efficacy in acute mania. In contrast, carbamazepine has been shown to be effective in multiple placebo-controlled studies of acute mania, and has an FDA indication for acute mania.

There is one maintenance randomized trial of oxcarbazepine in prevention of mood episodes in
bipolar illness. Compared to placebo, it was ineffective.

There are no randomized trials of oxcarbazepine in bipolar depression.

There are randomized data supporting benefit of carbamazepine for prophylaxis, but it too has not been studied much in acute bipolar depression.

**Licarbazepine**

There’s an important twist to this story. Oxcarbazepine has an active metabolite, licarbazepine. This metabolite is the reason why oxcarbazepine would be effective. The parent compound, oxcarbazepine, is a prodrug; it has no efficacy itself. It only works through licarbazepine.

Since oxcarbazepine had been on the market for decades, and its patent life was ending, its manufacturer decided to try to patent its active metabolite licarbazepine. To that end, it conducted multiple placebo-controlled trials of licarbazepine in acute mania, thinking it would be the fastest way to bring that agent to the market.

Licarbazepine is not on the US market. If it had been shown to be effective, its manufacturer would have taken those data to the FDA for an indication for acute mania. That did not happen.

There is an important feature of the FDA indication process to appreciate here. If a drug receives an FDA indication, it must have at least two positive trials showing that it is effective. It may have any number of negative trials as well, but at least two of those trials must be positive for the FDA to grant an indication, which allows a company to market and sell that product for that purpose.

A pharmaceutical company is obligated to provide all its data on all its studies, positive and negative, to the FDA, if it seeks and obtains an indication. It isn’t under any obligation to publish any of those data, which are patent protected and considered proprietary. Typically what happens is that companies publish their positive data as prominently as possible, and market them extensively. Negative data either are not published, or are published as quietly and discreetly as possible, and certainly aren’t marketed.

What happens if a drug is studied for an indication but it doesn’t work at all? All its studies are negative. Well, in that case a company would have no reason to seek an FDA indication, because it would be denied, given proof of inefficacy of its drug. In that case, the company simply would drop the whole process, and would not take those data to the FDA.

What then happens to those data, to the proof of inefficacy? The FDA has no access to such data, because they were never brought to the FDA for evaluation. The company is under no obligation to publish those data, and in fact they are private, proprietary data which are protected under US law. Who would know about those data? Company employees, obviously. Otherwise, the only outsiders who might know would be scientific consultants from the academic world. In those settings, though, the consultants have to sign confidentiality agreements such that they cannot publish or even talk about the private property (data) to which they become privy.
Which brings us back to licarbazepine. It was studied in acute mania in multiple placebo-controlled trials. That much is publicly known. It wasn’t taken to the FDA to seek an indication. This would not occur if the drug had shown efficacy. The PL editor has spoken to academic consultants, who have seen the licarbazepine data. Within the constraints of not breaking US law, those consultants couldn’t confirm or deny the inefficacy of licarbazepine, but they implied that the process provides the answer: If it was effective, it would have been taken to the FDA for an indication.

This process highlights a problem for the clinician:

If a drug works, you’ll hear about it, loud and strong. You’ll be marketed extensively.

But if a drug doesn’t work, even if it’s proven to not work, you may never be told.

PL is telling you: Licarbazepine very likely is proven ineffective in acute mania. And by extension, oxcarbazepine is proven ineffective.

Summary

What does this all mean for oxcarbazepine? It should be clear that the clinical research data for its efficacy is very weak, and if anything, mostly proves inefficacy. These clinical research data are the most directly relevant data as to deciding whether to use this agent or not. These clinical data contrast with clear data of efficacy with carbamazepine in acute mania and probably prophylaxis.

The only remaining rationale for using oxcarbazepine is the pure chemical analogy hypothesis. But we’ve seen how weak that claim is. On those grounds, we should use chlorpromazine to treat depression, and imipramine to treat mania and schizophrenia.

Biological speculation is unscientific and dangerous. In this case, it’s proven false.

The PL Bottom Line

- The biological speculation of oxcarbazepine efficacy based on carbamazepine efficacy is false and illogical. On that logic, imipramine and carbamazepine would be interchangeable, as would imipramine and chlorpromazine. All those agents have opposite clinical effects.

- Oxcarbazepine has little clinical research data evidence of efficacy.

- Its active metabolite, licarbazepine, was studied in acute mania and likely proven ineffective.

- Oxcarbazepine, in contrast to carbamazepine, likely is ineffective in bipolar illness.

PL Reflection

There is only one thing that I dread: not to be worthy of my sufferings.

Dostoevsky
**Study of the month: Oxcarbazepine maintenance efficacy**


The only randomized trial for long-term prevention

There is only one randomized maintenance trial of oxcarbazepine in bipolar illness, conducted in Spain.

**Method**

55 patients with bipolar illness on lithium were randomized to oxcarbazepine versus placebo added. They were in remission but had experienced two or more mood episodes in the prior year.

**Results**

Time to a first mood episode was similar in both groups, being 19.2 weeks with oxcarbazepine versus 18.6 weeks with placebo. Patients were followed for one year. Relapse rates into a full mood episode were lower with oxcarbazepine than placebo (38% versus 59%), but the difference wasn't statistically significant.

**Discussion**

The main result here is the time to an event, which is the basis of survival analysis. How long did it take until the patient relapsed? The answer was that it was the same for oxcarbazepine as for placebo.

What about the apparent lower rate of mood episode relapse? This could be relevant, and a larger study might or might confirm it. But we don't have any replication studies to assess the matter.

This is the only randomized placebo-controlled maintenance study of oxcarbazepine in bipolar illness. Long-term treatment with this agent is not based on acceptable amounts of scientific evidence, since these very limited data aren't meaningful enough to support such long-term use in a routine or common manner.

**The PL Bottom Line**

- Oxcarbazepine was ineffective in prevention of mood episodes in bipolar illness, equivalent to placebo in time to relapse.
- Therefore, oxcarbazepine is disproven as a “mood stabilizer,” if by that term we mean drugs proven to prevent mood episodes.

---

**PL Reflection**

Thankfully Sigmund Freud was spared knowing the concentration camps from the inside. His subjects lay on a couch designed in the plush style of Victorian culture, not in the filth of Auschwitz. There, the “individual differences” did not blur, but, on the contrary, people became more different; people unmasked themselves, both the swine and the saints.

Viktor Frankl
**Clinical Tip**

Treatment of akathisia: Use propranolol ER, not generic propranolol.

Standard propranolol only has a half of life of about 4 hours. Even if dosed twice or thrice daily akathisia will break through. There is a generic extended release version that can be given once at night. It comes in 60, 80, and 120 mg pill sizes. Start at 60 mg at night, and move up as needed. Check pulse before you start and increase dose if needed to a pulse that remains at 60 or above.

---

**PL Reflection**

“Most esteemed Lady, I have to disappoint you. I am not going to say ‘yes’ or ‘no’, nor shall I deal out question marks...It is quite evident that you...try in a visionary way to complete my fragments, build them into a structure....I feel you too might have slipped away from me to the system-builders, to Jung, or rather to Adler. But through the ego-libido you have observed how I work, step by step, without the inner need for completion, continually under the pressure of the problems immediately on hand and taking infinite pains not to be diverted from the path....in spite of advancing age I am not in a hurry.”

Sigmund Freud, private letter to Lou Andreas Salome, 1917
Drug of the Month: Trazodone
The perfect insomnia drug?

Biological mechanism

Trazodone is a serotonin reuptake inhibitor (SRI) with partial serotonin receptor 1 (5HT1a receptor) agonism.

Clinical efficacy

Trazodone is FDA indicated for major depressive disorder, not insomnia. It was developed originally in the late 1980s as one of the first SRI antidepressants. It was found to have little to no sexual dysfunction, but it was too sedating at antidepressant doses. This weakness became its strength, as it began to be used ubiquitously as an add-on treatment for insomnia, which was a side effect of other SRIs. Over the years, it has evolved into a standard treatment for insomnia, even though there are no randomized studies which prove its efficacy for primary insomnia, and it has no FDA indication for insomnia. Since it doesn't affect GABA receptors, unlike other sedatives, it isn't addictive.

Effects on sleep

There is a belief that trazodone improves sleep cycles, uniquely so among sedatives, the rest of which (including benzodiazepines and zolpidem and newer agents) either worsen sleep stage efficiency or are neutral at best. Specifically, the other agents add about half an hour of sleep but at the cost of less restorative deep stage sleep (stages 3 and 4). Trazodone instead appears to improve sleep efficiency and increases those deep sleep stages.

One blinded study found that trazodone increases total sleep time by about 50 minutes, which is about double most other sedatives. Further deep stages 3 and 4 sleep are increased from about 19% at baseline and with placebo to about 31% with trazodone. Another study found 37 minutes increased total sleep with trazodone, and an increase in deep sleep stages from 56 minutes to 87 minutes. In sum, consistently replicated randomized data indicate that trazodone improves sleep efficiency, unlike all other sedatives.

Dosing

At 50-100 mg/d, trazodone is sedating and used for sleep. Antidepressant effects occur in the 200-400 mg/d range. In bipolar illness, such doses could be destabilizing and/or cause mania.

Side effects

The main side effects are sedation and possible priapism.

The PL Bottom Line

• Trazodone improves sleep cycles, in contrast to all other sedatives.
• It isn’t addictive.
• Higher doses may produce antidepressant effects, for better or worse (e.g., bipolar illness).
A 48-year-old woman presented in referral after failing to respond to many different antidepressants and amphetamines and benzodiazepines. She had been diagnosed with major depressive disorder (MDD), adult attention deficit disorder (ADD), and generalized anxiety disorder (GAD). She had been treated for about 20 years with one serotonin reuptake inhibitor (SRI) or another. She had some improvement at times, but then she would have anxiety and depressive symptoms again. She was functional, able to work, even somewhat successful in her profession, but with great struggle. She felt that she could achieve even more if she didn't have so much anxiety and depression.

In prior evaluations, doctors had noticed some mood lability, but no definable hypomanic or manic episodes. She had refused to consider lithium due to its weight gain and stigma.

She had marked inattention, which led to the diagnosis of adult ADD and long-term treatment with a range of amphetamines, which helped her function at work. Anxiety was also treated with long-term clonazepam, which had mild benefit.

She also had been diagnosed with narcolepsy because she had periods where she would go for one week with much less sleep than usual, but then would fall asleep suddenly during the daytime. She denied manic symptoms during those one-week periods. She had severe insomnia most of the time, and had taken many sedating medications, with little benefit.

In her family history, she reported a lot of anxiety and depression but denied bipolar illness or schizophrenia.

She had occasional suicidal ideation (SI) but never had made an attempt. On evaluation, she was treated with oxcarbazepine 600 mg/d, fluoxetine 5 mg/d, Adderall (amphetamine/dextroamphetamine mixture) 20 mg/d, clonazepam 2 mg/d, and mirtazapine 10 mg at night.

On evaluation, the patient was very anxious, agitated, nervous, labile, worried, and had a number of depressive neurovegetative symptoms (low energy, interest, sad mood, poor concentration, and occasional SI). These symptoms had been present for months in a worsened state, and were present at least to a mild degree most of the time in the past year.

The entire history was based on the patient's self-report.

The PL consultant made the following observations: The patient's self-report is not sufficient for a dependable denial of past hypomanic or manic episodes, due to the problem of lack of insight, as described in the last PL issue. Thus, there was doubt whether the patient indeed did not have bipolar illness. It could be that what was called narcolepsy reflected cyclic manic/hypomanic episodes, which the patient couldn't describe in DSM-level detail. The recurrent decreased need for sleep that was described only occurs in manic/hypomanic episodes, not in narcolepsy, which is not a condition with weekly cyclic episodes, separated by periods of absence of narcolepsy symptoms.

The PL consultant raised the idea that the patient has “manic” symptoms, defined in the pre-DSM manner as “psychomotor excitation.” Clearly, this...
patient is highly psychomotor excited, with marked agitation and lability, at the same time as she has clinical depression. This is the classic presentation for “mixed depression” as defined by Koukopoulos. As discussed on the PL website, mixed depression is treated by stopping all antidepressants and amphetamines, and using dopamine blockers and/or second messenger modifiers (mood stabilizers).

In other words, the PL consultant argued that the diagnoses of MDD, GAD, and ADD had been tried for 20 years, and had failed. It was time to have a different working diagnosis, and then to test it. The most likely working diagnosis, on the rationale given above, was “manic-depressive illness,” meaning recurrent mixed depressive episodes. Using DSM terminology, the diagnosis would still be MDD. Using non-DSM terminology, it would be manic-depressive illness.

In this case, the implication of that approach to mixed depression would be to taper the patient off fluoxetine, Adderall and mirtazapine. Clonazepam is neutral in its effect, probably not helping or hurting at this time.

Oxcarbazepine would be stopped and replaced with an effective second messenger modifier, on the grounds that oxcarbazepine likely is ineffective as described in this issue of PL. Such scientific evidence of inefficacy is supported by the patient’s limited benefit with the agent.

As the patient is taken off the three antidepressants/amphetamines, the PL consultant recommended adding a dopamine blocker like aripiprazole or ziprasidone or asenapine or lurasidone (all do not have metabolic syndrome or cardiac risks or weight gain). If the patient improved, then the question of lithium or valproate could be considered for long-term prevention of mixed states.

Another option would be to add low-dose lithium or valproate at present, holding off on the dopamine blockers. In the opinion of the PL consultant low dose valproate (about 500-750 mg/d) might be the most effective single treatment, with lower dose limiting weight gain. “Therapeutic” blood levels are irrelevant because we are not treating mania.

All these recommendations are made not because the patient has “bipolar” illness, as a DSM term, but because the patient has mixed depressive states. As noted on the PL website, mixed states are equally common in “unipolar” and “bipolar” illness, both of which can be seen as variations on the same disease: manic-depressive illness. This perspective is the original Kraepelinian view.

There was some resistance on the part of the treating clinicians to the PL consultation. It was argued that a very rapid diagnosis of bipolar illness had been made, and that the PL consultant wanted to treat everyone with mood stabilizers.

The PL consultant responded that bipolar illness was not being diagnosed, but rather manic-depressive illness, which is a larger and broader construct, as discussed above and in the PL website.

Further, the PL consultant suggested that there are more drugs in psychopharmacology than only antidepressants and amphetamines. This patient had been treated for two decades with only those two main classes of drugs (plus benzodiazepines). Why not try the two main drug classes – dopamine blockers and second messenger modifiers - that had not been used, at least on
pragmatic grounds? While doing so, it makes sense not to just add one drug after another, but to stop some of the drug classes that had not helped much, especially since those agents can worsen some of her symptoms (amphetamines worsen anxiety, SRIIs cause mania/agitation).

This case is not presented with follow-up, but it is described here so that PL readers can think themselves about such complex mixtures of symptoms. It also is presented as a common scenario where patients are not exposed to standard second messenger modifiers, but only receive disproven ones, like oxcarbazepine. The case also highlights importance of stopping symptomatic treatments, like amphetamines, in patients with marked anxiety and depressive symptoms, which cause inattention.

**Clinical Corner**

*What’s a “working diagnosis”?*

The above case raises the question of the relevance of the concept of a “working diagnosis.” This old medical tradition appreciates two basic features of clinical practice: the uncertainty of diagnosis, but also its importance.

Your treatment is only as good as your diagnosis. Making a diagnosis is central to Hippocratic medical practice (defined not as “first do no harm”, which Hippocrates never said; but rather defined as treating diseases not symptoms). If you don't work hard to make a diagnosis, and then obtain the scientific evidence regarding its treatment, then you are practicing unscientific medicine. If you only treat symptoms, you are practicing unscientific medicine. This is a matter of medical history: for 2500 years physicians treated symptoms with treatments (mostly bloodletting). The basic insight of modern scientific medicine, inaugurated by thinkers like William Osler about a century ago, is that we should organize symptoms into diagnoses reflecting disease, and then treat the disease, not the symptoms directly.

So the first step is to realize the importance of diagnosis. It isn't optional. We have to make a diagnosis so that we can know if, and how, to treat.

The second step is to acknowledge uncertainty. There’s always uncertainty in clinical diagnosis, even in parts of medicine with blood tests. There are false positives and false negatives even with HIV tests, much less with clinical diagnoses. So what do we do?

Since uncertainty is ubiquitous, since it is the norm in the practice of clinical medicine, it isn't an excuse for refusing to diagnose. It isn't good enough to say: I’m not sure what the diagnosis is, so I won't diagnose. I'll just treat the symptoms. This gets back to the Hippocratic insight that treating symptoms leads to more harm than good. (See the PL website for a discussion of this idea).

The concept of a “working diagnosis” provides a solution. The clinician says to herself: I’m not sure what the diagnosis is, but I'll make my best judgment. I'll diagnose what is most likely.

The next step also is important. The working diagnosis must be tested. It must be ruled in or ruled out. It isn't enough to make it, and then refuse to change one’s mind for 20 years. Test it. In psychiatry, we don't have blood tests, but one test (albeit sometimes inconclusive) is medication treatment. Give the proven treatment for your working diagnosis. If the patient improves notably and persistently, you've confirmed the diagnosis. If not, you've raised doubts about it, and, at some point, you should move to the next diagnosis on your list.
Curbside Consults

Questions/comments/cases from you

Question: What do you think of bupropion (Wellbutrin) for bipolar depression?

PL: Like all antidepressants, bupropion is ineffective in bipolar depression, proven to be equivalent to placebo. Thus PL thinks it should not be used. It is popular because it has been shown to have a low manic switch rate. This is probably because it is given at low dosages. But even if it doesn’t cause mania, it is ineffective, and thus there is no point in using it.

It should be noted that bupropion is an amphetamine in its structure. Hence it isn’t surprising that it causes weight loss and enhances sexual libido and causes anxiety. All amphetamines can cause mania and destabilize bipolar illness, as shown in some studies. Bupropion may be less potent than other amphetamines, and thus less likely to have those harmful effects in bipolar illness, especially at low doses. But if it is dosed high enough, it will cause mania and it will destabilize bipolar illness.

Question: Is there a good scale to assess affective temperaments?

PL: We recommend the TEMPS scale (Temperament Evaluation scale of Memphis Pisa San Diego). It is very well-validated and studied to assess hyperthymia, cyclothymia, and dysthymia. 39 item and 50 item self-report versions are available via the internet.

PL Reflection

Science is generally taken as meaning either (a) the exact sciences, such as chemistry, physics, etc., or (b) a method of thought which obtains verifiable results by reasoning logically from observed fact.

If you ask any scientist, or indeed almost any educated person, ‘What is science?’ you are likely to get an answer approximating to (b). In everyday life, however, both in speaking and in writing, when people say ‘science’ they mean (a).

Science means something that happens in a laboratory: the very word calls up a picture of graphs, test-tubes, balances, Bunsen burners, microscopes....

Scientific education for the masses will do little good, and probably a lot of harm, if it simply boils down to more physics, more chemistry, more biology, etc., to the detriment of literature and history....

Scientific education ought to mean the implanting of a rational, sceptical, experimental habit of mind. It ought to mean acquiring a method — a method that can be used on any problem that one meets — and not simply piling up a lot of facts.

George Orwell