THE CARLAT REPORT PSYCHIATRY

A CME Publication

Subscribe today!
Call 866-348-9279

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Chris Aiken, MD
Editor-in-Chief

Volume 18, Issue 8
August 2020
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Traumatic Brain Injury

A Guide to Online and Overseas Pharmacies — 1

Expert Q&A: — 1
Jonathan Silver, MD
Assessing and Treating Traumatic Brain Injury

Silexan: A Novel Anxiolytic — 5

Tables:
- Medications for Cognitive Symptoms of TBI — 3
- Silexan for Generalized Anxiety Disorder — 5
- Know Your Online Pharmacy — 7

Research Updates: — 6
- Insight in Therapy: Still Relevant After All These Years
- A New Antipsychotic for Bipolar Depression

CME Test — 7

Learning Objectives

After reading these articles, you should be able to:

1. Instruct patients on best practices for evaluating and using online and overseas pharmacies.
2. Identify the efficacy of Silexan for treating generalized anxiety disorder.
3. Assess and treat cognitive symptoms of traumatic brain injury.
4. Summarize some of the current research on psychiatric treatment.

A Guide to Online and Overseas Pharmacies

Kristen Gardner, PharmD. Clinical Pharmacy Specialist in Behavioral Health at Kaiser Permanente, Colorado.

Dr. Gardner has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Highlights From This Issue

Most symptoms of traumatic brain injury improve when sleep is addressed, but daytime rest is ill advised.

Medications for generalized anxiety disorder tend to have a small effect size. Silexan, a proprietary extract of lavender, is an exception.

Online pharmacies save costs, and we have resources to make sure they are safe and secure.

You've probably seen these scenarios in your practice. A patient doing well on Latuda can't afford the $800 monthly cost with a new insurance plan. Another patient on disulfiram can't find the medication because there is a nationwide shortage. Someone else expresses interest in medications used in other countries like amisulpride, tianeptine, or agomelatine. Can an online pharmacy help these patients "thread the needle"?

Background

US prescription drug costs have been increasing for decades. But e-commerce, where you can purchase just about anything on the internet, has also gotten more prevalent. So why not obtain prescriptions that way too? The first online pharmacy launched in 1999. As of 2015, there were more than 35,000 online pharmacies operating across the

Continued on page 4

Q&A With the Expert

Assessing and Treating Traumatic Brain Injury
Jonathan Silver, MD

Clinical Professor of Psychiatry at New York University School of Medicine. Co-editor of the Textbook of Traumatic Brain Injury *3e (APA, 2019).*

Dr. Silver has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: How does a head injury differ from a traumatic brain injury (TBI)?

Dr. Silver: A head injury is not the same as a brain injury. Not all blows to the head result in an injury to the brain. TBI means there was an injury to the brain caused by the application of external force. That differentiates it from other kinds of brain injury, such as stroke and anoxic brain injury.

TCPR: How do we know if the brain is injured after a patient hits their head?

Dr. Silver: That's where the second criterion for TBI comes in. To diagnose a TBI, there has to be some evidence of an alteration in brain function at the time of the injury. Usually it would be within moments of the injury. Some experts allow more delay, such as hours or even 1–2 days, but the further you get away from the event, the more likely it is that something else is the cause of those symptoms.

Continued on page 2

Expert Interview

Continued from page 1

TCPR: What are the symptoms to look for?

Dr. Silver: They can range from a coma, where the person is not arousable, to amnesia, where they don't remember things before or after the injury. With milder injuries, patients may feel dazed or confused, or see stars. We tend to see mild injuries more often in sports. Some people use the word "concussion" for those mild injuries, but that term is not well defined. A person with a mild TBI will often complain of cognitive problems, fatigue, depression, insomnia, irritability, and physical symptoms like headache, dizziness, tinnitus, and heightened sensitivity to noise and light, as well as to the effects of alcohol.

TCPR: How long do those problems last after a mild TBI?

Dr. Silver: The best results are with sports concussions in a healthy group of individuals, such as Division I athletes. In that group, 90% get better in days and 95% improve within 4 weeks (McCrea M et al, *JAMA* 2003;290(19):2556–2563). It can last longer in other groups, like 1–3 months. When a patient complains of ongoing problems for months or years after the injury, it's likely that they stem from multiple causes, including psychiatric and physical causes. Post-traumatic stress, depression, and anxiety disorders can start after a concussion and cause concussive-like symptoms to persist. Another cause is neck problems.

TCPR: Neck problems?

Dr. Silver: Whiplash and neck injury can result in the same symptoms of concussion: dizziness, poor concentration, insomnia, and fatigue. Everyone with a head injury should have a physical exam of the neck for range of motion, tenderness, and muscle spasms.

TCPR: We're hearing a lot about chronic traumatic encephalopathy (CTE) from repetitive concussions, such as in football players. How does that differ from TBI?

Dr. Silver: TBI is an event, while CTE is a process that unfolds over time. We know a lot less about CTE, but it's not due to a single concussion; it appears to be the result of repetitive concussions in some people. We don't yet know who is susceptible to CTE and what makes them susceptible, but lots of people are exposed to TBI and the incidence of CTE is relatively low, so it's likely this is a small minority. It might be that people who develop CTE have a genetic susceptibility to dementia that's unleashed by the repetitive injuries. We are at the early stages of research here.

> **"Patients with TBI do respond to antidepressants, but you may have to be more careful about certain side effects, like fatigue or, with bupropion and the tricyclics, seizures. Very often their mood will improve, but problems with concentration, fatigue, sleep, or apathy often persist, so we end up using some novel medications to target those symptoms."**
>
> Jonathan Silver, MD

Treatment of TBI

TCPR: TBI can cause a lot of symptoms. Where do you start?

Dr. Silver: I usually address sleep first. Other symptoms tend to improve if the patient is sleeping better. If behavioral approaches don't work for the insomnia, I'll often use trazodone or mirtazapine. I try to avoid benzos because they can impair memory and balance, but I do occasionally prescribe them.

TCPR: Any special tips for treating depression after a TBI?

Dr. Silver: Patients with TBI do respond to antidepressants, and you can use just about any antidepressant in this population. You may have to be more careful about certain side effects, like fatigue or, with bupropion and the tricyclics, seizures. Very often their mood will improve, but the problems with concentration, fatigue, sleep, or apathy often persist. And that's where we end up using some novel medications to target those symptoms that may be unique to this population.

TCPR: Like what?

Dr. Silver: I try to start with the easiest one first, which is usually amantadine. This medication was developed to treat the flu, but it has been studied in TBI and in other conditions with fatigue like multiple sclerosis. Amantadine has some mild stimulant properties, but it's not a controlled drug. It seems to help attention, fatigue, and irritability. I start with 100 mg in the morning, and then after a week I'll go to 100 mg in the morning and 100 mg in the afternoon. Sometimes I'll go to 300 mg/day, but if it doesn't work after 200 mg/day, I'll usually stop.

TCPR: And if amantadine doesn't work?

Dr. Silver: I may try a psychostimulant like methylphenidate or dextroamphetamine varieties, or a wakefulness-promoting agent like modafinil or armodafinil (*Ed note:* These last two are rarely covered by insurers but are

Continued on page 3

EDITORIAL INFORMATION

Publisher: **Daniel Carlat, MD**

Editor-in-Chief: **Chris Aiken, MD**

Deputy Editor: **Talia Puzantian, PharmD, BCPP,** professor, Keck Graduate Institute School of Pharmacy, Claremont, CA

Executive Editor: **Janice Jutras**

Editorial Contributor: **Kristen Gardner, PharmD**

Editorial Board:

Ronald C. Albucher, MD, clinical associate professor of psychiatry, Stanford University, Palo Alto, CA

Osman M. Ali, MD, staff psychiatrist, VA North Texas Health Care System, associate professor, department of psychiatry, UT Southwestern Medical Center, Dallas, TX

Richard Gardiner, MD, psychiatrist in private practice, Potter Valley, CA

Alan D. Lyman, MD, child and adolescent psychiatrist in private practice, New York City, NY

Brian McCarthy, MSN, PMHNP-BC, nurse practitioner in private practice, The Mood Treatment Center, Winston-Salem, NC

James Megna, MD, PhD, DFAPA, director of inpatient psychiatry, professor, departments of psychiatry, medicine, and public health & preventive medicine, SUNY Upstate Medical University, Syracuse, NY

Michael Posternak, MD, psychiatrist in private practice, Boston, MA

Glen Spielmans, PhD, associate professor of psychology, Metropolitan State University, St. Paul, MN

Marcia L. Zuckerman, MD, outpatient psychiatrist, Hallmark Health, Medford, MA; clinical assistant professor in psychiatry, Tufts School of Medicine

All editorial content is peer reviewed by the editorial board. Dr. Carlat, Ms. Jutras, Dr. Aiken, Dr. Albucher, Dr. Ali, Dr. Gardiner, Dr. Gardner, Dr. Lyman, Mr. McCarthy, Dr. Megna, Dr. Posternak, Dr. Puzantian, Dr. Spielmans, and Dr. Zuckerman have disclosed that they have no relevant financial or other interests in any commercial companies pertaining to this educational activity.

This CME/CE activity is intended for psychiatrists, psychiatric nurses, psychologists, and other health care professionals with an interest in the diagnosis and treatment of psychiatric disorders.

Expert Interview

Continued from page 2

available for $20–30/month through GoodRx.com). I start at a very low dose, like methylphenidate 5 mg/day. I'll raise it every couple of days based on response, but if it doesn't work at 15 mg/day I'll usually switch to a dextroamphetamine-based stimulant like Adderall or Vyvanse.

TCPR: How do you treat apathy?

Dr. Silver: We have not had much success there. Apathy is usually something that bothers the relatives more than the patient. The family is upset that the patient is withdrawn and unmotivated but the patient is usually, well, apathetic—they do not care. We often try dopaminergics out of the theory that this is a dopamine deficiency. They just don't tend to be very successful, including the stimulants and pramipexole.

TCPR: How do you treat memory in TBI?

Dr. Silver: There's very good Class I evidence for the acetylcholinesterase inhibitors: rivastigmine (1.5–12 mg/day) and donepezil (5–10 mg/day) (Silver JM et al, *Brain Inj* 2009;23(2):123–132). These can improve memory in people with significant deficits after a TBI, and the patient usually notices a difference. I usually start with donepezil 5 mg/day for 1 month, then 10 mg/day; if the patient is not doing better after 2 months, I stop it. (*Ed note:* See the table on this page.)

TCPR: How do you assess improvement in memory?

Dr. Silver: You could use rating scales or test cognition. While those approaches are worthwhile, I tend to rely more on functioning and the observation of the patient and significant others. If there's no functional change, then the treatment is probably not making a difference. Ask the patient and the family if they see a difference. The relatives will often give you a different picture.

TCPR: Irritability is another nonspecific symptom that can come on after a TBI. How do you address that?

Dr. Silver: Yes, irritability and aggression are common problems in this population. One of the first medications I start with is buspirone. It actually has good evidence for irritability in TBI and little risk. I start with 7.5 mg bid and go to 15 mg after 1 week, and it can go up to 30 mg bid. After buspirone, the choice depends on which other symptoms are present. If the patient is irritable and depressed, I'd start with an SSRI. Often the irritability will respond to fairly low doses like escitalopram 10 mg/day or sertraline 25 mg/day. Amantadine is another option for irritability in TBI. It's a good choice if the patient also has fatigue and attentional problems. And then there's beta-blockers like propranolol. These have the best evidence of efficacy for irritability after TBI, with propranolol doses up to 640 mg/day.

Medications for Cognitive Symptoms of TBI

Name	Class	Dose	Cognitive Targets
Amantadine	NMDA antagonist and dopaminergic	50–300 mg	Arousal, attention, executive function, irritability
Bromocriptine	Dopamine agonist	2.5–90 mg	Arousal, working memory, executive function
Citicoline	Natural supplement with nootropic effects	1,000 mg (eg, Cognizin by Bestvite, $30/month)	Declarative memory
Donepezil	Acetylcholinesterase inhibitor	5–10 mg	Attention, processing speed, working and declarative memory
Dextroamphetamine	Stimulant	5–60 mg (target 0.6 mg/kg/day)	Attention, processing speed
Methylphenidate	Stimulant	5–60 mg (target 0.6 mg/kg/day)	Arousal, attention, processing speed, working and declarative memory
Modafinil & armodafinil	Wakefulness-promoting agent	Modafinil 50–400 mg qam Armodafinil 50–250 mg qam	Arousal
Rivastigmine	Acetylcholinesterase inhibitor	1.5–12 mg	Declarative memory

Source: Adapted from Silver J et al (2018), Textbook of Traumatic Brain Injury *3e*

TCPR: Any risks with propranolol?

Dr. Silver: Most patients tolerate it well. It lowers heart rate and blood pressure, but that effect tends to level off after 300 mg/day. It can cause fatigue and decrease exercise tolerance, and sometimes there are sexual side effects.

TCPR: Amantadine was once called the best-studied medication for irritability in TBI, but some recent studies have been disappointing. Where does it stand now?

Dr. Silver: As I mentioned before, the best evidence is still for beta-blockers. The two best studies with amantadine in irritability after TBI were both done by Flora Hammond. The first was a single-center study that showed a significant improvement with amantadine compared to placebo (n = 76). The second study found no difference. It was a larger (n = 168), multisite study, and it had a large placebo effect. There was significant therapeutic interaction between the staff and the subjects, which makes everyone get better. So it was a "failed" study, and it's hard to know what to do with that. In my experience, I've not been too impressed with amantadine in irritability, but it is certainly worth trying (Hammond FM et al, *J Head Trauma Rehabil* 2014;29(5):391–399; Hammond FM et al, *J Neurotrauma* 2015;32(16):1230–1238).

TCPR: What about antipsychotics for irritability?

Dr. Silver: They could be useful if the irritability is due to mania or a psychotic condition, but there are actually no controlled trials of antipsychotics in TBI. It is important to rule out medications and substances that could be

Continued on page 4

Expert Interview

Continued from page 3

contributing to irritability in TBI, like alcohol, benzos, opioids, or steroids. Interestingly, the psychostimulants do not make irritability worse in TBI, but they don't improve it either.

TCPR: Are people with TBI more sensitive to side effects?

Dr. Silver: I do hear that said (and I've said it myself countless times!), but I'm not sure how true it is. It is true for the anticholinergic medications because those have more cognitive side effects. There's some evidence that people with TBI are more sensitive to neurological side effects on lithium or antipsychotics, such as extrapyramidal side effects (EPS). If I use an antipsychotic, I often start with one that carries a lower risk of EPS, like quetiapine. Outside of that, there is no evidence that people with TBI are more sensitive to side effects. It's still wise to start low and go slow, but you still have to get to the same therapeutic dose in people with TBI.

TCPR: What lifestyle advice do you give to these patients?

Dr. Silver: The best things that patients with TBI can do are diet, sleep, and exercise. I'll add mindfulness and meditation to that list. All those are good for your brain. Exercise helps recovery after mild TBI, and there are good studies showing that. The worst advice is to rest after a brain injury. Patients may need to reduce their workload and activity for a few days, but strict rest worsens the outcome (Thomas DG et al, *Pediatrics* 2015;135(2):213–223). They need to keep moving—doing so helps the brain recover.

To learn more, listen to our 8/17/20 podcast, "Treatment Tips for TBI." Search for "Carlat" on your podcast store.

TCPR: Thank you for your time, Dr. Silver.

A Guide to Online and Overseas Pharmacies

Continued from page 1

globe, and 1 in 4 online shoppers order prescription medications online. They value the perceived lower cost and higher privacy, convenience, and autonomy (Mackey TK and Nayyar G, *Br Med Bull* 2016;118:115). Each of those factors can improve adherence—particularly cost, which prevents 1 in 3 adults from taking their medications regularly (Kirzinger A et al, *JAMA* 2019;322(15):1440). But there is a dark side to the boon of online ordering.

The best and the worst

Ideally, an online pharmacy will follow the laws and regulations of both the country where its operations are occurring and the country it's shipping to. The key sign that an online pharmacy is legit is if its web address ends with the ".pharmacy" domain. This means the pharmacy participates in on-site inspections from the National Association of Boards of Pharmacy (NABP). Certified pharmacies may also display the Verified Internet Pharmacy Practice Sites (VIPPS) seal of approval. The VIPPS program recently transitioned into the ".pharmacy" program to prevent companies from forging the seal. So far, ".pharmacy" domains cannot be faked.

We don't recommend using online pharmacies that lack NABP/VIPPS certification. If patients go that route on their own, the "Know Your Online Pharmacy" table on page 7 lists red flags to watch out for.

Unfortunately, most online pharmacies are illegitimate, rogue, or illicit. A stunning 96% of them either don't comply with regulations or aren't subject to regulatory review, licensure, or certification. In particular, they often sell imported medications worldwide, and it's hard to know whether imported drugs meet FDA standards for safety and efficacy since they bypass closed, regulated supply chains.

The safety concern associated with these drugs is real—the World Health Organization has determined that more than 80% of medicines are counterfeit in some countries. The market for counterfeit drugs is worth an annual $431 billion and surpasses almost everything else in the underground economy, including prostitution, human trafficking, and illegal weapon sales. Additionally, drugs sold by illicit online pharmacies may contain dangerous substances such as rat poison, mercury, or antifreeze; be improperly stored; be old/expired; or be poorly manufactured in unsafe conditions or with low-quality ingredients. Besides the health risks, rogue online pharmacies may lack safeguards to protect consumers' finances, personal data, and electronic devices.

Online Canadian pharmacies are safe, right?

Most online pharmacies that advertise as Canadian actually have no connection to the country at all. When a US citizen purchases medications through a "Canadian" pharmacy, chances are high that the person will receive a drug that wasn't approved by Canadian regulatory agencies. Even Canadian government and organizational officials are concerned about US importation of drugs from Canada. Since Canada is struggling with similar issues, they have borrowed NABP's ".pharmacy" program. However, only pharmacies licensed in Canada dispensing Health Canada–approved products to Canadian citizens are eligible for a ".pharmacy" domain. Ultimately, it is illegal for non-US pharmacies to import drugs into the US.

How to protect your patients

Patients may not tell you that they are using online pharmacies, so open up the conversation by asking them where they plan to purchase their medications. Those who are more likely to go the online route include older adults, indigent patients, and those with financial problems or coverage limitations.

If patients tell you they plan to order online, give them a list of safe options. Two websites with reliable lists are the VIPPS program (www.nabp.pharmacy/programs/digital-pharmacy/accredited-facilities) and BuySafeRx (www.safe.pharmacy/buy-safely). Alternatively, patients can check if an online pharmacy is safe by entering its internet address at www.VerifyBeforeYouBuy.org.

Continued on page 7

Silexan: A Novel Anxiolytic

Chris Aiken, MD. Editor-in-Chief of TCPR.
Practicing psychiatrist, Winston-Salem, NC.

Dr. Aiken has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Patients with generalized anxiety disorder (GAD) often look to medications for help, but GAD is one of the disorders where medications are likely to disappoint. Effect sizes tend to fall in the small range (0.2–0.3) with meds for GAD, including SSRIs, SNRIs, buspirone, and pregabalin (Lyrica). Only the benzodiazepines have an effect in GAD that's big enough for the casual observer to notice, with an effect size of 0.5 (Gomez AF et al, *Expert Opin Pharmacother* 2018;19(8):883–894). So when an oral extract of lavender called Silexan outperformed paroxetine in GAD with a large effect size of 0.87, it caught my attention.

What is Silexan?

Silexan is a branded extract of lavender that was developed by Schwabe Pharmaceuticals in 2002. Its active ingredients—linalool and linalyl acetate—comprise 71% of the oil, with the remaining 29% made up of trace amounts of over a hundred other compounds from the lavender plant. Silexan is regulated as a prescription and licensed for anxiety in 14 countries. In the US, it is available over the counter as CalmAid, through Schwabe's "Nature's Way" line.

Silexan's pharmacologic properties are more in line with conventional medications than with most CAM therapies. Like pregabalin, it inhibits calcium channels; like the benzos, it has GABA-ergic effects; like ketamine, it is an NMDA antagonist; and like buspirone and vortioxetine, it is a serotonin-1A agonist. The serotonin-1A agonism is probably the most relevant mechanism, judging from animal studies where Silexan's anxiolytic effects were measured after blocking the various mechanisms (Baldinger P et al, *Int J Neuropsychopharmacol* 2014;18(4):pyu063).

The research

The best evidence of Silexan's benefit in GAD comes from a large (n = 539) randomized, double-blind controlled trial that compared two doses of Silexan (80 mg or 160 mg/day) to paroxetine 20 mg/day and placebo. This 10-week study had four important outcomes:

1. Both doses of Silexan worked significantly better than paroxetine and placebo ($p < 0.01$) on the primary outcome (Hamilton Anxiety Rating Scale) as well as on secondary measures of depression, sleep quality, and quality of life.
2. The effects were dose dependent, with an effect size of 0.4 for the 80 mg dose and 0.5 for the 160 mg dose.
3. Half of the patients on the 160 mg dose achieved remission.
4. Silexan was as well tolerated as placebo.

Three smaller controlled trials have tested Silexan in GAD, mixed anxiety-depression, and subsyndromal anxiety. A Cochrane-style meta-analysis of all the trials found a medium effect size (0.67) for anxiety and a large effect (0.87) in studies that exclusively enrolled patients with GAD (Generoso MB et al, *J Clin Psychopharmacol* 2017;37(1):115–117). One of those studies found that low-dose Silexan (80 mg/day) was comparable to low-dose lorazepam (0.5 mg/day) after 6 weeks in patients with GAD.

The strengths of these studies include double blinding, intent-to-treat analysis, and restriction of adjunctive medications or psychotherapies. On the other hand, most were manufacturer funded and came from a single academic center (University of Vienna).

Silexan's benefits are usually apparent after 2 weeks, and they continue to build over the next 3 months. Although not directly sedating, Silexan does improve sleep quality, an effect that appears to be secondary to its anxiolytic properties (Seifritz E et al, *J Psychiatr Res* 2019;115:69–74).

Safety

Silexan has no known withdrawal effects, addictive potential, or drug interactions. Burping was the only side effect that emerged in the clinical trials of 1165 subjects. In animal models, lavender oil is neuroprotective (Sánchez-Vidaña DI et al, *Neurosci Lett* 2019;701:180–192).

Lavender oil is considered safe for consumption by the FDA and NIH, with one exception. Some of the ingredients have weak estrogen-like properties, and there are rare cases of breast development in adolescent boys and early breast development in young girls who were exposed to lavender oils or aromatherapy (Ramsey JT et al, *J Clin Endocrinol Metab* 2019;104(11):5393–5405). I would avoid it in children under age 18.

There are no reports of hormonal problems in adults, but patients with a history of estrogen-sensitive cancers should probably avoid it unless approved by their oncologist. The risk here is unclear, as lavender extracts are actually being explored as treatments for breast cancer (Al-Sheddi ES, *Asian Pac J Cancer Prev* 2019;20(10):2943–2949).

Aromatherapy

The aromatherapy form of lavender is what inspired the Silexan research. The plant's oils have been used in this way to calm the nerves and induce sleep for centuries. These benefits have nothing to do with lavender's aroma, as mice that are unable to smell respond equally well to its anxiolytic effects. My hunch is that the lavender mist delivers the same active compounds as Silexan through the intranasal route. Lavender oil can also be rubbed on the skin, but this method is not as effective as the aromatherapy. Based on indirect comparisons,

Continued on page 8

Silexan for Generalized Anxiety Disorder	
Product	Nature's Way CalmAid ($24/month for 160 mg dose)
Dosing	Start 80 mg qhs, increase to 160 mg qhs after 1 week if needed; most patients require 160 mg qhs, but milder cases may recover fully with 80 mg
Side effects	Lavender-flavored burping, sedation
Half life	9 hours
Drug interactions	None known, but more study is needed
Relative contraindications	Avoid in children under age 18 (gynecomastia risk)

Research Updates IN PSYCHIATRY

PSYCHOTHERAPY

Insight in Therapy: Still Relevant After All These Years

REVIEW OF: Jennissen S et al, *Am J Psychiatry* 2018;175(10):961–969

STUDY TYPE: Systematic review and meta-analysis

What makes psychotherapy work? Contenders abound, including the therapeutic alliance, behavior change, and cognitive restructuring. This meta-analysis looked at the role that insight plays in psychotherapy outcomes.

The authors defined insight as the ability to understand 1) associations between past and present experiences, 2) patterns in relationships, and 3) the relationships between stress, emotions, and psychological symptoms. Their literature review included psychotherapy studies in adults that measured an outcome consistent with that definition. Inclusion criteria were otherwise broad, requiring that the study involved adults who sought therapy for any psychological condition.

From over 13,000 papers initially identified, only 23 met the full criteria. Although the authors' definition of insight was based on psychodynamic theory, a variety of psychotherapies were included, with psychodynamic, supportive, and cognitive behavioral the most common.

The primary outcome was the effect size of the association between insight and psychotherapy outcomes. After employing a battery of meta-analytic techniques, the authors calculated a correlation coefficient of 0.3 for this association. That's considered a moderate correlation, about the same as the correlation between age and blood pressure. It is also in the same range reported for other well-established psychotherapy moderators, such as the therapeutic alliance, positive regard, and empathy.

Strengths of the study include a large sample involving 1,112 total subjects and reliance on a standardized meta-analytic methodology. Although broad in scope, a weakness was the lack of a consensus measure of insight (18 instruments used, with a mix of clinician and self-report tools) or of outcome (27 outcome scales, most of them quantifying symptoms) among the studies included. In short, such a wide range of methods and measures allowed in the included studies "may be viewed as a threat to validity," in the authors' own words.

Beyond the technical difficulties in definition and measurement, the authors also acknowledge a statistical truism: that correlation does not prove causation. For example, it is possible that insight was not the causative agent, and that the gains in insight were secondary to other changes such as improvements in psychological symptoms or relationships.

TCPR'S TAKE

This study lends some empirical support to the age-old idea that insight is a mechanism of change in psychotherapy. When patients are aware of their own role in the problems they bring to therapy, they are better equipped to find adaptive solutions.

—Greg Sazima, MD. Dr. Sazima has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

To learn more, listen to our 8/24/20 podcast, "What Is Insight?" Search for "Carlat" on your podcast store.

BIPOLAR DEPRESSION

A New Antipsychotic for Bipolar Depression

Lumateperone (Caplyta) just hit the pharmacy shelves with FDA approval in schizophrenia (see *TCPR* March 2020), and its manufacturer is pursuing further approval for bipolar depression. So far they've completed two phase III trials—one negative and one positive—and the positive one was presented in poster form by Suresh Durgam and colleagues at the International Society for Bipolar Disorders in June 2020.

The positive study was a controlled trial that randomized 377 patients to placebo or lumateperone 42 mg/day without titration (the same dose used in schizophrenia). Lumateperone began to separate from placebo after 1 week on the primary outcome measure (the Montgomery-Åsberg Depression Rating Scale), and those improvements continued throughout the 6-week trial ($p < 0.0001$ with intent-to-treat analysis). The main side effects were nausea and fatigue, but sleep also improved on this sedating antipsychotic. Consistent with the schizophrenia studies, the rates of akathisia and weight gain were low and not significantly different from placebo.

A strength of the study was the inclusion of bipolar II patients, who represented 20% of the sample. Although depression is more common in bipolar II than I, most antipsychotics have only been tested in bipolar I depression. Exceptions are quetiapine, which worked in bipolar II patients, and cariprazine (Vraylar), which did not. Lumateperone worked in the subset with bipolar II, but its effects were more pronounced in the bipolar I group.

Details on the negative trial were not available, but it was a smaller study (178 patients) with a similar design. Joseph Calabrese, one of the principal authors, reported that lumateperone still upheld a moderate effect size (0.56) when the results of the two studies were combined.

TCPR'S TAKE

Lumateperone is worth trying when other options for bipolar depression have failed, but insurance coverage will be difficult without FDA approval for that indication.

—Chris Aiken, MD. Dr. Aiken has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

To learn more, listen to our 8/31/20 podcast, "Existential Despair in Bipolar Depression: An Interview with Nassir Ghaemi." Search for "Carlat" on your podcast store.

CME Post-Test

To earn CME or CE credit, log on to www.TheCarlatReport.com with your username and password to take the post-test. You must answer 75% of the questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be completed within a year from each issue's publication date. The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Carlat CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Carlat CME Institute maintains responsibility for this program and its content. The Carlat CME Institute designates this enduring material educational activity for a maximum of one (1) *AMA PRA Category 1 Credits*™ or 1 CE credit for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/

This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Learning Objectives (LO) are listed on page 1.

1. Which of the following types of pharmacies licensed in Canada are eligible for a ".pharmacy" domain? (LO #1)
   - [ ] a. Pharmacies dispensing Health Canada-approved products to Canadian citizens only
   - [ ] b. Pharmacies licensed in Canada dispensing Health Canada-approved products to North American countries only
   - [ ] c. Pharmacies licensed in Canada dispensing Health Canada-approved products worldwide
   - [ ] d. Both a and b

2. Silexan may pose risks in which of the following populations? (LO #2)
   - [ ] a. Patients who currently use tobacco products
   - [ ] b. Patients with a history of alcohol or drug addiction
   - [ ] c. Patients under age 18
   - [ ] d. Patients over the age of 65

3. According to Dr. Silver, amantadine is a good first-line choice for treating which symptoms of TBI? (LO #3)
   - [ ] a. Declarative memory and apathy
   - [ ] b. Attention and irritability
   - [ ] c. Apathy and attention
   - [ ] d. Declarative memory and irritability

4. One of the weaknesses of a 2018 study on the association between insight and outcome of psychotherapy was its small sample size. (LO #4)
   - [ ] a. True
   - [ ] b. False

5. Which of the following is a clue that an online pharmacy website might be legitimate? (LO #1)
   - [ ] a. The site ends with a .ru domain
   - [ ] b. The site can be confirmed at NeedyMeds.org
   - [ ] c. The site offers shipping worldwide
   - [ ] d. The site displays the Verified Internet Pharmacy Practice Sites seal of approval

6. In addition to generalized anxiety disorder, Silexan can also have a positive effect on _____. (LO #2)
   - [ ] a. Migraine headaches
   - [ ] b. Obsessive thoughts
   - [ ] c. Sleep quality
   - [ ] d. Tremors

A Guide to Online and Overseas Pharmacies

Continued from page 4

Other ways to lower costs

Before patients turn to internet pharmacies, there may be other ways to lower their costs. Advise patients to check out reputable websites like GoodRx.com, NeedyMeds.org, RefillWise.com, or SaveOnMyMeds.org. These websites do the legwork to compare local prescription costs. Some of them (NeedyMeds.org and SaveOnMyMeds.org) also connect to manufacturer patient assistance programs. Asking pharmacies for "the cash price" of a drug may yield lower costs than using insurance. There may even be payment plans or financial assistance programs available from insurers or health systems.

Consolidate doses and make use of half-tablets if they can be safely cut, especially if the drug has flat pricing. Just make sure that you write the prescription the way you intend the patient to take it—it's fraudulent to raise the dose artificially. For example, if you intend the patient to take Latuda 60 mg daily, don't prescribe 120 mg 1 tablet daily #30 and tell the patient to cut the pills in half in order to save on copays. A 90-day supply will usually lower costs, both for patients on insurance and those who are paying for the medication out-of-pocket.

Know Your Online Pharmacy

Red Flags	Safety Clues
.com, .net, and .ru websites	".pharmacy" verified or VIPPS certified
No prescription required	Prescription required
Absent, incomplete, or unidentifiable physical address and contact information	Verifiable physical address and contact information
Lacks verifiable pharmacy license in the country in which it operates	Verifiable pharmacy license in its country of operation
Ships worldwide	Operates within the consumer's country of residence
Offers deep discounts or cheap prices	Sells medication approved in the consumer's country
Sends unsolicited emails or texts	Offers licensed pharmacist consultation

TCPR VERDICT: Legitimate online pharmacies offer convenience, privacy, and cost savings. Many of your patients are already using them, so open up the conversation and let them know where to find reliable sources that are either VIPPS certified or part of the ".pharmacy" program.

THE CARLAT REPORT
PSYCHIATRY
P.O. Box 626
Newburyport, MA 01950

This Issue:
Traumatic Brain Injury
August 2020

Next Issue:
When to Use Lithium
September 2020

Silexan: A Novel Anxiolytic

Continued from page 5

aromatherapy works faster than oral Silexan, but Silexan is more potent after several weeks of treatment (Sayed AM, *Gen Hosp Psychiatry* 2020;64:33–40).

How to use Silexan

Silexan is a reasonable choice for patients who have not responded to FDA-approved treatments for GAD. Patients who prefer natural approaches could use it first-line. For others, the natural aspect will invite skepticism, and they may benefit from a discussion of Silexan's pharmacologic properties.

I started recommending Silexan in 2016 and have treated 505 patients with it, most with GAD or a mood disorder with anxious distress. My experience has been in line with the research, with the best results in pure GAD. Most patients were taking long-term benzos, and many spontaneously reduced their benzo dose on their own after starting it. Patients often forget to reorder Silexan, and when they come off it, it usually takes a few months for the anxiety to return. The change is so gradual that many don't notice it. This is where careful tracking with rating scales (which can be as simple as having patients rate their anxiety from 1–10) and trials on and off Silexan come in handy.

TCPR VERDICT: Most CAM therapies do not have robust effects, but Silexan is an exception. Consider it in adults with generalized anxiety disorder.

To learn more, listen to our 8/10/20 podcast, "What Works for Treatment-Resistant Anxiety?" Search for "Carlat" on your podcast store.