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Editor-in-Chief

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This issue of *TCPR* may fulfill your state licensing board's "end of life care" CME requirements!

IN THIS ISSUE

Focus of the Month:
End of Life Care

Learning objectives for this issue: **1.** Describe the basics and benefits of palliative care. **2.** Explain existential psychotherapy. **3.** Detail specific psychiatric considerations in palliative care. **4.** Understand some of the current findings in the literature regarding psychiatric treatment.

A Primer on Palliative Care

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Dr. Neale has disclosed that she has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

With its goals of relieving suffering and improving patients' quality of life, psychiatry plays a central role in palliative care. In fact, psychiatry was one of the 10 specialty boards involved in the creation of the new subspecialty of Hospice and Palliative Medicine (HPM), approved by the American Board of Medical Specialties in 2006. Physicians who have completed residency in any of these 10 fields are eligible to complete a HPM fellowship and become HPM certified. The knowledge and skills gained through psychiatric training are recognized as valuable assets for a palliative care physician.

What is "Palliative Care"?

The World Health Organization defines palliative care (PC) as "an approach that improves the quality of life of patients and their families facing the problems associated with life threatening illness, through prevention of and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychological and spiritual." To meet these multidimensional needs, PC is usually provided by a team including physicians, nurses, social workers, and chaplains. Patients can receive PC at any time along the trajectory of a serious

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Existential Psychotherapies: An Introduction

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Dr. Tong has disclosed that he has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

Psychotherapy provided near the end of a patient's life focuses on existential themes. While the term "existential" conjures up questions like "why am I here?" and issues about meaninglessness, death, and our limited lifespan, existential therapy is about much more: an awareness of oneself, one's freedom to make choices, and one's capacity to remove obstacles to "authentic existence."

Over the years, existential therapy has taken many forms, resulting in confusion and vagueness as to what exactly is an existential approach. On a popular level, the orientation has been routinely dismissed as nothing more than an amorphous and scattered way of "being" obviously left over from the tofu-brained New Age era of the 1960s.

Existential therapy is not traceable to any single founding figure, as was the case with other popular forms of psychotherapy like psychoanalysis or cognitive therapy. Furthermore, there are many existential therapies.

To date, we have the European traditions: existential analysis, daseinsanalysis, existential-analytic therapy, logotherapy, and Laingian therapy. Over on the American side are existential-humanistic therapy, reality therapy, Gestalt therapy, client-centered therapy, existential-integrative therapy, and the brief existential therapies. Last but not least, there are those approaches with an "Eastern" emphasis, such as existential contemplative therapy and my own existential Taoist psychotherapy. In the words of Mick Cooper, existential therapists are "more intertwined in their philosophic orientation" and vary more widely in their actual techniques.

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A Primer on Palliative Care
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or life-threatening illness. (This is distinguished from hospice care, a subset of PC that is reserved for end of life treatment.) PC can also be provided in conjunction with treatments aimed at life prolongation. For example, a patient with metastatic breast cancer may be treated by an oncologist who focuses on cancer treatment while a PC team focuses on management of symptoms (pain, nausea, shortness of breath, depression, anorexia, fatigue, spiritual distress, etc) and assists with advance care planning.

In the United States, PC is generally provided as an inpatient or outpatient consultation. Providers may request a PC consultation to assist with clarification of the patient's goals of medical care, symptom management, communication between the medical team(s) and the patient and family, prognostication in advanced illness, advance care planning, and end of life (EOL) care. For instance, a common consultation is to help a patient with advanced liver disease to understand the severity of the illness and treatment options, and to manage pain, shortness of breath, and nausea.

The ultimate goals of consultation are to treat symptoms of advanced illness and to assist patients and families in understanding their prognosis, in expressing the goals (or most important factors) in their medical care, and in receiving medical care that is aimed at achieving their goals of care. For example, is the patient with liver disease more interested in staying in the hospital to receive intravenous therapies of marginal benefit or in returning home to spend time with family and friends?

Hospice Care

Hospice care, by contrast, is a specific type of palliative care for patients nearing the end of life. In the United States, hospice refers to a healthcare benefit provided through Medicare Part A or private insurance. A patient is eligible to receive hospice care if two physicians certify that he or she has a life expectancy of six months or less if the "disease runs its usual course." In addition, the patient must choose to trade standard Medicare Part A (inpatient) coverage for the hospice benefit, which covers medical care that is usually provided in the home and is focused on comfort and relief of suffering rather than life prolongation. Patients with any end-stage disease (heart failure, dementia, COPD, HIV, cancer) are appropriate for hospice referral. Hospice care is the form of PC that most physicians are familiar with; however PC is a much broader discipline.

Discussing End of Life Care with Patients

In addition to focusing on the relief of suffering, palliative providers are often involved in discussions about advance care planning and EOL care. For example, we may discuss prognosis, current treatment options, and options for future care with a patient with end-stage COPD. Specifically we would talk about what is most important to the patient in the time they have left to live and how their medical care can help them to achieve these goals. We would review if the patient is interested in intubation/ICU care or care that is entirely focused on their comfort in the event of a future COPD exacerbation.

There is a robust body of literature demonstrating that the majority of patients want to have these discussions with their providers, yet fewer than 50% of patients actually do (Reilly et al, *Arch Intern Med* 1994:154(20):2299–2308). Providers often cite barriers to having these conversations, such as a lack of training, lack of time, and concern that such discussions may harm patients or "take away their hope."

Multiple studies have evaluated the effects of these conversations on patients' treatment choices, quality of life, and mental health in addition to the effects on caregivers' quality of life, mental health, and perception of the patient's death. The *Coping With Cancer* study was a multisite prospective cohort study of 332 patients with metastatic cancer who progressed through first-line chemotherapy, and their caregivers (Wright et al, *JAMA* 2008:300(14):1665–1673). The 37% of patient/caregiver dyads who reported having a discussion about end of life care with their providers were compared to the dyads who reported not having these conversations. The patients who had the discussions were more likely to prefer medical care focused on relief of pain and suffering over life-extending treatments. These patients also were more likely to complete a DNR order and less likely to be admitted to the ICU, receive mechanical ventilation, or undergo a resuscitation attempt. Interestingly, patients who received less aggressive care experienced a *better quality of life* without a decrement in survival time. EOL discussions were not associated with patients feeling depressed, sad, terrified, or worried or meeting DSM criteria for a psychiatric disorder.

Their caregivers benefitted, too. Caregivers of patients who received aggressive care in the last week of life were more likely to develop major depressive disorder, experience regret, feel unprepared for the patient's death, and report poorer quality of life and health after the patient's death. This study supports the concept that EOL discussions and less aggressive EOL medical care are associated with better quality of life among patients and their caregivers.

Patients report that the manner in which EOL discussions are held is as important as the content of the discus-

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A Primer on Palliative Care

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sions. According to current research, cancer patients in Western countries want realistic, truthful information that is delivered with a focus on what can be done (symptom management, emotional support, practical support, and maintenance of dignity). They value discussions in which the provider explores realistic goals as a means of fostering hope. Such goals might include control of pain and shortness of breath so patients can spend more time talking with their families. Patients feel that a discussion of what the future may hold should be well-timed. They want the information to be given when loved ones can be present and when the provider can spend an adequate amount of time with them. Lastly, patients value respect for their emotional state and an acknowledgement of the emotional, spiritual, and existential impact of having a life-threatening illness.

TCPR'S VERDICT: Given the heavy emotional burden associated with advanced illness, there has always been a significant role for psychiatry in PC. An important demonstration of this role is the inclusion of psychiatry as a specialty supporting the subspecialty of Hospice and Palliative Medicine. The challenge ahead is to further develop strategies for advancing the collaboration between providers of palliative and psychiatric care.

Existential Psychotherapies: An Introduction

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Furthermore, the credibility of existential approaches is just now beginning to be elevated in the eyes of those preoccupied with "evidence-based" (ie, empirically validated) support for the viability of any and all psychotherapies (think of the exacting requirements of HMOs and health insurance companies for reimbursement of treatment fees.) Writings by Schneider and others allude to the need for relevant peer-reviewed studies. The paucity of published empirical outcome work remains, but could well be viewed as a temporary state (Schneider KJ, Bugenthal JFT, and Pierson JF. *The Handbook of Humanistic Psychology.* Sage Publications: Thousand Oaks, CA; 2001).

Nuts and Bolts of Existential Thought

Since its inception in the 1950s, the existential movement in psychology and psychiatry has attempted to forge an understanding of people based not only on observable behavior patterns (*à la* DSM), but also on their unique condition as living beings who exist, have a life narrative, and are always in the dynamic process of changing and becoming. The existential attitude or *posture* (my preferred term) is one that transcends *and* includes systematic theoretical orientations. Its focus is on "lived experience," which is unfortunately overshadowed by the predominant emphasis on capturing the essence of personhood in theoretical and diagnostic boxes. Central historical figures in the field have posited the existence of an innate human tendency to resist or revolt against such dehumanizing objectification and reductionism.

The word existential frequently evokes themes of gloom and doom, alienation, ambiguity, and uncertainty, concepts that are recurrent in the works of existentialism's European forebears. In contrast to the American humanistic overemphasis on being eternally positive, existential therapists continually stress the need to not run from the dark side of existence. In David Richo's remarkable book, *The Five Things We Cannot Change* (Boston, MA: Shambhala Publications; 2006), the reader is challenged to embrace certain fundamental unchangeable facts of life: (1) everything changes and ends; (2) things do not always go according to plan; (3) life is not always fair; (4) pain is a part of life; and (5) people are not loving and loyal all the time.

The existential challenge for both client and therapist is how to live life in the face of certain inescapable "givens" of existence. Although it's said that the only certainties in life are death and taxes, the existential givens vary from one author to the next. Irvin Yalom, for one, has proposed a list of four definitive sources of "ontological insecurity:" death, freedom, isolation, and meaninglessness.

Central to the ontological givens is *finiteness.* Very simply, this is the concrete reality that life as we know it will end. For millions of aging Baby Boomers, the End of Days looms large. As the years grow short, there is the inevitable isolation resulting from the loss of significant others as well as the deterioration of mental and physical capacities. On the other end of the chronological spectrum, tens of thousands of "millennials" (18 to 30 year olds) are being pummeled by chronic post-economic-downturn unemployment or under-employment, moving back in with parents, and inability to start their own families. Even more important, they are roundly bewildered and destabilized by having gobs of time on their hands. A young client seeing me at the lowest end of my sliding scale fees bemoaned: "I live in a great country that prizes freedom to choose but I have nothing to choose *from!"* All this has added up to nothing short of a crisis of meaning.

Existential Therapy

What, then, is existential therapy all about? The overarching aim is the achievement of a "genuine encounter," that is, to be truly present with another human being. Authentic healing, transformation and change begins, proceeds, and ends with this. Schneider, for one, speaks of such core aims in existential-humanistic therapy to (1) help clients become present to themselves and others; (2) help clients to experience ways in which they mobilize and block themselves from fuller presence; (3) help clients take responsibility for the choices that they make in their lives; and (4) help clients choose ways to face, and not avoid, the existential givens—finiteness, ambiguity, isolation, and meaninglessness (see also Breitbart W et al, *Can J Psychiatry* 2004;49:366–372).

My mentor Murray Bilmes once said that "the most difficult thing in life is to see it as it really is." As often as not, this is frequently the starting point of psychotherapy with an existential orientation. Put another way, the challenge before the client is to call things in one's life by their real names. Many if not most contemporary Americans refuse to acknowledge that some things they experience as inevitable in life are actually the outcome of acts of agency—ie, having made choices. In this vein, existentialists refer to existential guilt—guilt the result from

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Q&A With the Expert

This Month's Expert

The Role of Psychiatry in Palliative Care

William Breitbart, MD

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Dr. Breitbart has disclosed that he receives income from books he has published. Dr. Balt has reviewed this article and has found no evidence of bias in this educational activity.

TCPR: Dr. Breitbart, please tell us the unique role psychiatry plays in palliative care.

Dr. Breitbart: The goals of palliative care are to provide physical symptom control throughout the entire course of an illness, from the diagnosis of a life-threatening illness all the way through the advanced stages and the last periods of life, and to follow families through the bereavement process. Psychiatric palliative care helps to expand that focus beyond pain and physical symptom control to include other aspects of quality of life, such as the psychiatric, psychosocial, existential, and spiritual aspects of palliative care. These may ultimately culminate for some patients in being able to have a peaceful acceptance of death or acceptance of the life that they lived so that they can face death with peace.

TCPR: What are some of the concerns that lead to psychiatric consultation in the palliative care setting?

Dr. Breitbart: There are basically three categories of problems that warrant attention from a psychiatrist. One is the psychiatric and psychological disorders that occur as comorbid disorders in people with physical illnesses. The second is symptom clusters that we have expertise as psychiatrists addressing. And then the third is existential distress that is so common in all of us.

TCPR: Let's start with these psychiatric comorbidities. What specific challenges do you encounter when people have psychiatric complaints in the context of medical illnesses?

Dr. Breitbart: Anxiety is one of the most challenging complaints. If you do a survey of the various symptoms that patients experience with cancer or HIV disease, for instance, anxiety is up there—in the 80% to 90% range (Breitbart W & Alici Y, *Harv Rev Psychiatry* 2009;17:361–376). The real challenge in the medical setting is trying to determine in fact whether we're seeing anxiety related to a psychiatric source or anxiety from a medical source. For instance, it is quite common to see patients get anxious when experiencing a pulmonary embolism. Some of the medications that are used to treat nausea can also cause akathisia and severe anxiety.

TCPR: Etiology is probably an important consideration in depression, too?

Dr. Breitbart: The challenges in depression are actually a bit more complex because the *DSM-IV* criteria for a diagnosis of depression were established in physically healthy patients. For the last 20 or so years, those of us in the psychosomatic medicine world have been trying to extrapolate those criteria to help us make diagnoses of clinical depression in a physically ill population. There are many symptoms of clinical depression that can be produced by, for instance, cancer or its treatment. It is very difficult to make a diagnosis of depression with any kind of specificity when, for instance, symptoms of appetite loss, weight loss, feelings of hopelessness, psychomotor retardation, and others can be caused by the illness or the treatment itself.

TCPR: How do you address this?

Dr. Breitbart: There are a number of ways that we have been trying to deal with that problem over the years. We have experimented with the use of a set of substitution criteria—something called the "Endicott Substitution Criteria" that replace nonphysical symptoms for some of the physical symptoms of depression. Another very convenient method that has been developed over the last 10 years is what we call an "increased threshold approach" to diagnosing depression in the cancer population or advanced illness population. Instead of requiring the main threshold criteria symptom of depressed mood for a couple of weeks or more, plus four more symptoms (for a total of five), we just increase the threshold to seven. The thresholds for depression or anhedonia plus six more symptoms, and that pretty much correlates with the specificity of diagnosing clinical depression that you would get with using the Endicott substitution criteria. Another issue is that it is sometimes difficult to determine whether someone is having a major depressive episode that is essentially the same type of disorder that one would see in a physically health person, or if it is caused by medical etiologies. In other words, the progression of cancer itself can lead to depression.

TCPR: Does this make a difference in treatment?

Dr. Breitbart: Fortunately, many of the treatments are quite similar in terms of the psychotherapy and the psychopharmacologic interventions. There have been about a dozen trials of traditional antidepressants that show that even in terminally ill and advanced cancer populations, those medications work regardless of etiology (Rhondali W et al, *Eur J Hosp Pharm* 2012;19(1):41–44).

TCPR: Delirium is a big concern in palliative care. Please tell us about that.

Dr. Breitbart: Delirium is a primary focus of psychiatric intervention and care, particularly in the hospital or in the hospice palliative care unit setting. For comparison, the prevalence of depression is somewhere in the range of 15% to 25% in the palliative care setting, while the prevalence of delirium, particularly in the last weeks of life, may rise as high as 85% (Breitbart W & Alici Y, *JAMA* 2008;300(24):2898–2910). The challenges are in terms of the goals of care. Most of the time when we treat delirium, we hope to achieve a state in which patients are awake and alert and able to communicate with their physician and the family. When patients are dying that goal may not be achievable, so we are often faced with a dilemma: do I keep a patient somewhat awake but dis-

tressed and hallucinating; or do I work with the patient and the family to keep that patient comfortable, but perhaps a bit sleepy or sedated?

TCPR: When you're treating patients with delirium at the end of life, what types of treatments might you give or withhold?

Dr. Breitbart: The principles for managing delirium are the same no matter what the stage. You want to approach delirium by doing two things at the same time: You want to try to identify and treat or remove the sources, and you want to control the symptoms of delirium, which is sometimes done with antipsychotic drugs. However, when delirium appears in the last weeks of life, you may decide that you do not want to be as aggressive as you would in someone who is, for instance, getting a bone marrow transplant or has a fever or sepsis and is delirious. But you can still use psychopharmacologic interventions to try to control the symptoms, and most of the time you will be able to achieve the goal of the patient being somewhat awake and alert and able to communicate.

Many of these interventions—meaning-centered psychotherapy in particular—have been shown to help maintain sense of meaning, hope, and lessen the fear of death

William Breitbart, MD

TCPR: Can you speak about the subtypes of delirium?

Dr. Breitbart: Despite the fact that delirium can be categorized into various subtypes based on things like motoric function or arousal disturbance, only about half of patients with delirium have what is called an agitated, hyperactive, or hyperaroused delirium (what most people think of when they hear "delirium"). About 50% of patients with delirium in the medical setting, and particularly in the palliative care setting, have hypoaroused or "quiet" delirium. However, this population is as distressed as the hyperactive, hyperaroused, or agitated delirium patients (Breitbart et al, *Psychosomatics* 2002;43(3)183–194). We have been able to show with studies of antipsychotic interventions that those patients respond just as well to treatment as the hyperactive or agitated delirious patients.

TCPR: Please tell us about concerns like fear of death, the meaning of life, and other existential concerns and distress. How do we help patients facing the end of life deal with these?

Dr. Breitbart: We have started to move away from the notion that all existential and spiritual concerns about death and being able to look back and accept the life that one has lived are purely the domain of the chaplain or the clergy in palliative care. Certainly, if someone is having a crisis of religious faith, involving a chaplain or clergy is reasonable. But most patients are not having these crises of religious faith; what they are having is a crisis of meaning in their life that is caused by not being able to complete their life trajectory. So when we think of spirituality in our clinical research group we think it has components of both religious faith and of personal meaning. So we deal with spiritual or existential concerns and stress in patients by focusing on concepts such as meaning and purpose, and by helping patients come to some sense of coherence about the meaning in their lives, leaving a legacy.

TCPR: This relates to the idea of dying with dignity?

Dr. Breitbart: Yes, there are now about three or four clinical interventions that focus on meaning, dignity, or end of life task completion. There is meaning-centered psychotherapy from our group, dignity-conserving therapy from a group led by Harvey Chochinov from Canada, and end of life task completion work developed by Karen Steinhauser from Duke. David Kissane in Australia developed something called cognitive existential therapy, focused on cognitive distortion and dealing with existential issues. Probably the granddaddy of all of these interventions was David Spiegel's supportive expressive psychotherapy in women with advanced breast cancer where they not only provided support, but focused on detoxifying death.

TCPR: Very interesting. Are these therapies evidence-based?

Dr. Breitbart: There are multiple interventions that have been developed and tested in randomized controlled trials and are now tools that palliative care physicians, psychiatrists, psychologists, social workers, and other mental health professionals in palliative care settings can apply to help patients deal with concerns of profound loss of meaning, demoralization, end of life task completion, leaving a legacy, conserving dignity, being able to live until they die, and being able to deal with what lies beyond. Many of these interventions—meaning-centered psychotherapy in particular—have been shown to help maintain sense of meaning, hope, and lessen the fear of death (Breitbart W et al, *Psycho-Oncology* 2010;19(1):21–28; Breitbart W et al, *J Clin Oncology* 2012;30(12):1304–1309). We just finished the second edition of the *Oxford Handbook of Psychiatry and Palliative Medicine* that is now in paperback, and it really covers every aspect of psychiatric palliative care from diagnosis to assessment to some of these psychotherapies.

TCPR: Can you briefly comment on the role of the psychiatrist in alleviating the suffering of caregivers, like family members, nursing staff, and others?

Dr. Breitbart: We have learned from the caregiver literature that caregivers are extraordinarily distressed and have high rates of comorbid psychiatric disorders. There are a lot of practical concerns: financial impact of caregiving, physical exhaustion, skills they are not prepared for that they need to suddenly learn related to nursing, and so forth. We are developing a caregivers program in our Department of Psychiatry at Sloan-Kettering that focuses on the needs of caregivers and family members. We also have a family therapy program and a couples program under the umbrella of a caregiver program. We provide one-to-one caregiver intervention as well, which often moves into a bereavement phase. And we are developing an adaptation of psychotherapy for caregivers to help them deal with the burden of caregiving by focusing on the enhancement of meaning in their lives through the caregiving act. I think one would look to the caregiver literature for patients with Alzheimer's disease and dementia as an example as the first population in which the problems of caregivers have been identified and interventions for caregivers have been developed. And we are catching up, but there are some unique aspects to this type of distress and caregiving burden in the palliative care setting as well.

TCPR: Thank you, Dr. Breitbart.

Research Updates IN PSYCHIATRY

Section Editor, Glen Spielmans, PhD

Glen Spielmans, PhD, has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

BIPOLAR DISORDER

Is Low Dose Lithium Effective in Bipolar Disorder?

Although it remains one of our oldest and most effective drugs, lithium has become less popular for the treatment of bipolar disorder in the last two decades. The recent LiTMUS trial compared outcomes in bipolar disorder when all subjects took non-lithium mood-stabilizing medication, while half were also randomized to low-dose lithium. The others remained on their existing medications ("optimized personal treatment," or OPT) alone. LiTMUS involved 283 subjects with bipolar disorder I (77%) or II. All were considered by their psychiatrists to be candidates for lithium treatment. The lithium group (N=141) was given 600 mg/d lithium for the first two months, with further adjustments up or down as necessary, while the rest remained on OPT alone.

After six months of follow-up, the authors found no significant advantage to lithium on the CGI-BP-S (clinical global impression for bipolar severity) scale. Scores decreased by only 1.22 points in subjects in the lithium+OPT group, versus 1.48 points in the OPT group. There was also no difference between the groups in the number of medication adjustments required by clinical need.

Was this a failure of lithium? Not necessarily. It's possible that lithium may simply not have been dosed appropriately. Mean lithium levels in the lithium+OPT group ranged between 0.43 and 0.47 mEq/L during the trial (as opposed to the >0.8 mEq/L recommended by most treatment guidelines). And even though the focus of the trial was on low-dose lithium, clinicians were free to increase lithium dose as much as they wished after the first two months. As a single-blind trial, it is also possible that prescribers may have been reluctant to increase lithium dose for fear of causing additional side effects. Finally, higher doses may only have been given to those subjects with more severe illness.

Overall, clinical outcomes were disappointing in both groups, with only one quarter of all subjects achieving remission (defined as CGI-BP-S <2 for two months). Symptomatic improvement ranged from 30% to 50% in both groups. The only metric on which the lithium+OPT group differed from OPT alone was in their lower use of atypical antipsychotics, which were prescribed to only 48.3% of the lithium-OPT subjects (vs. 62.5% of the OPT group) (Nierenberg AA et al, *Am J Psychiatry* 2013;170(1):102–110).

TCPR's Take: Lithium has a well-deserved position as a workhorse of modern psychiatry, and while this study's results seem to call that role into question, a "peek under the hood" shows that lithium may simply have been dosed too conservatively in this study. Notably, only a quarter of all subjects in this naturalistic, "real world" trial achieved remission while taking guideline-driven therapy (OPT), with or without lithium. And while it appears that patients on lithium were less likely to use atypical antipsychotics, it remains an open question whether higher doses of lithium may have produced better clinical outcomes than OPT.

DRUGS IN THE PIPELINE

Drugs Acting on Glutamate

You're probably hearing a lot of talk about glutamate receptors as a new target for psychiatric therapeutics. As the most abundant excitatory neurotransmitter in the brain, glutamate is thought to play a role in many psychiatric conditions. Some existing drugs act on the glutamate system (eg, lamotrigine and memantine), but more are likely on the way. In fact, several lines of evidence suggest that glutamate function may be disrupted in psychosis and in mood disorders.

Psychosis

Drugs like PCP and ketamine inhibit the NMDA receptor (one of the main glutamate receptor subtypes, others being the AMPA receptor and the metabotropic or "mGluR" receptors). When abused, these drugs can cause a schizophrenia-like syndrome, complete with positive, negative, and cognitive symptoms. Moreover, glutamate synapses also appear to develop abnormally in schizophrenia, and hypofunction of the NMDA receptor has been observed in later stages of the disease (Moghaddam B and Javitt D, *Neuropsychopharm* 2012;37:4–15). One theory of schizophrenia is that faulty NMDA receptors—present on inhibitory interneurons—are indirectly responsible for the overproduction of glutamate in the prefrontal cortex, where glutamate acts on non-NMDA receptors in a disorganized fashion, possibly contributing to psychosis.

Some new antipsychotics under development include drugs that enhance NMDA receptor function and thereby reduce cortical glutamate. Mechanisms of these drugs include the activation of secondary pathways like the metabotropic mGlu5 receptor on NMDA-containing cells (mGlu5 agonists) or the modulation of other metabotropic glutamate receptors found in the cortex (mGlu2/3 agonists). Also, since the NMDA receptor is a complex receptor with binding sites for co-activating molecules like the amino acid glycine, these sites are targets for so-called "allosteric modulators" which, when present, may enhance glutamate signaling at the NMDA receptor.

Each of these mechanisms represents a target of current drug development. Results, however, have been mixed. Perhaps the most promising, LY2140023, an mGlu2/3 agonist from Eli Lilly, failed a phase III trial late last year. Roche is developing a glycine transport inhibitor called bitopertin which has shown reductions in negative symptoms in phase II trials. Other trials have focused on sarcosine, a dietary supplement that also works as a glycine transport inhibitor. mGlu5 agonists are still in preclinical (ie, animal) testing. These and other glutamatergic drugs may find a place in the treatment of psychosis in the near future.

Depression

The NMDA receptor has also received a great deal of attention in the treatment of depression, spurred by the observation that subanesthetic doses of intravenous ketamine, an NMDA

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CME Post-Test

To earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer at least four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by Febuary 28, 2014. As a subscriber to *TCPR,* you already have a username and password to log on www.TheCarlatReport.com. To obtain your username and password or if you cannot take the test online, please email info@thecarlatreport.com or call 978-499-0583.

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Below are the questions for this month's CME post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning objectives are listed on page 1.

1. According to research by Reilly et al, which of the following statements is correct regarding discussions about advance-care planning and EOL care between patients and their doctors (Learning Objective #1)?

   [ ] a) Fewer than half of patients want to have these discussions, and fewer than half actually do
   [ ] b) Fewer than half of patients want these discussions, yet the majority have them anyway
   [ ] c) The majority of patients want these discussions, yet fewer than half actually do
   [ ] d) The majority of patients want these discussions, and more than half actually do

2. Existential theory can be said to focus on which of the following:

   [ ] a) The "lived experience," and the dynamic process of changing and becoming
   [ ] b) Redirecting maladaptive thoughts and behaviors
   [ ] c) Becoming a dispassionate observer of our private experiences and outer circumstances and simply accepting things as they are
   [ ] d) Emotional self-regulation

3. According to Dr. William Brietbart, the presence of delirium may be how high in the palliative care setting (LO #3)?

   [ ] a) 25% [ ] b) 45% [ ] c) 75% [ ] d) 85%

4. In the Nierenberg AA et al study of lithium, what was the change in points on the CGI-BP-S scale for the lithium + optimized personal treatment group (LO #4)?

   [ ] a) 1.22 point decrease [ ] b) 1.48 point decrease
   [ ] c) No change [ ] d) 1.22 point increase

5. Regarding glutamate agents for psychosis and depression, which statement is most accurate (LO #4)?

   [ ] a) NMDA antagonists are being studied for both psychosis and depression
   [ ] b) NMDA antagonists are being studied for psychosis, while NMDA-enhancing agents are being studied for depression
   [ ] c) NMDA-enhancing agents are being studied for psychosis, while NMDA antagonists are being studied for depression
   [ ] d) NMDA-enhancing agents are being studied for both psychosis and depression

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Research Updates

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antagonist, may have a rapid (within hours) and prolonged (up to two weeks) antidepressant effect (Zarate CA et al, *Arch Gen Psychiatry* 2006;63(8):856–864). The mechanism appears to involve the sprouting of neural synapses in the brain and the reversal of stress-induced changes (Li N et al, *Science* 2010;329(5994):959–964). Some hospitals and clinics have begun to provide this off-label treatment to patients with treatment-resistant depression.

Not surprisingly, the excitement surrounding ketamine has led to compounds believed to act similarly. One is GLYX-13, an NMDA partial agonist developed by Naurex, which showed promise in phase IIa trials. This intravenous agent boasts a similar time course of action as ketamine but fewer side effects. Another is AZD6765, an intravenous NMDA antagonist first developed by AstraZeneca as a neuroprotective agent for stroke patients. In treatment responders, sustained benefit isn't seen until three weeks, calling into question any advantage over current antidepressants. Phase IIb trials for each of these agents are currently under way. Other glutamatergic drugs being studied for depression include an mGlu2/3 antagonist (Roche), an mGluR5 antagonist (Roche), and NMDA antagonists which bind to specific subunits (particularly NR2B) of the NMDA receptor complex.

TCPR's Take: Currently available treatment options for psychosis and depression leave much to be desired. Lately, attention has been drawn to the glutamate synapse, with several drug companies jockeying to bring new glutamatergic drugs to market. These may represent a significant advance in psychiatric therapeutics, and might be useful adjuncts to existing treatments. Hopefully research will reveal the best use of these agents, specific patients who will benefit, and any possible side effects resulting from their use.

Existential Psychotherapies: An Introduction

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having wronged or cheated oneself, in contrast to neurotic guilt which is traceable to having wronged another person. Anything short of deep and thorough candid confrontation with one's self is tantamount to a compromise of one's own authenticity and autonomy.

Existential therapy attempts to enable this confrontation of oneself. The existential process may involve such specific procedures as: (a) clarifying choices and consequences; (b) sitting or being with the discomfort of powerful feelings and bodily sensations evoked by denied or buried memories; and (c) engaging in "more of the same" symptom behaviors that initially propelled the patient to seek therapy (paradoxic intention). Within the context of a safe "holding" therapeutic setting, the patient is gently and firmly challenged to confront the charge to make (or acknowledge) choices and to take responsibility for acting on those decisions.

TCPR'S VERDICT: Existential psychotherapies are grounded in the view that healing and change requires a genuine presence or authentic encounter between two human beings. Within this potent context, the patient is encouraged to confront, in an unwavering and uncompromising manner, the truth of his or her life situation, given both its inevitabilities and its possibilities.

Author's note: The website of my colleague Louis Hoffman provides an excellent introduction and a comprehensive range of useful resources on existential psychotherapy: http://bit.ly/14KYcgw

Next month in *The Carlat Psychiatry Report*: Medico-Legal Topics

This Month's Focus:
End of Life Care

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