As 2014 winds to a close, here’s a look back at the most relevant developments that took place in our field this year.

New Approvals of Drugs and Devices (US FDA)

**Contrave (Naltrexone-Bupropion)**
The US FDA approved Contrave—a combination of naltrexone and bupropion—as treatment for weight management in adults with a body mass index (BMI) of 30 or greater (obesity) or adults with a BMI of 27 or greater (overweight) who have at least one weight-related condition.

**Belsomra (Suvorexant)**
Suvorexant, marketed as Belsomra, is now approved for the treatment of insomnia (sleep onset and maintenance). Suvorexant is an antagonist at orexin 1 and 2 receptors and is the first such agent approved to treat insomnia.

**Hysingla ER (hydrocodone bitartrate)**
Hysingla ER is an extended-release opioid medication approved for use only to treat pain severe enough to require around-the-clock long-term opioid treatment and for which no alternative is available. Hysingla ER has properties that may reduce its abuse: it is difficult to crush, break, or dissolve, and also forms a viscous hydrogel that cannot be easily prepared for injection.

**Targiniq ER (oxycodone-naloxone)**
Targiniq ER is an extended-release/long-acting opioid medication with abuse-deterrent properties and is approved for use only to treat pain severe enough to require around-the-clock long-term opioid treatment and for which no alternative is available. When crushed or snorted, the naloxone blocks the euphoric effects of oxycodone.

**Bunavail (buprenorphine-naloxone)**
Bunavail (buprenorphine and naloxone) is approved for the maintenance treatment of opioid dependence. Bunavail is a buccal film that adheres to the inside of the cheek. Compared to Suboxone (sublingual formulation of buprenorphine and naloxone), Bunavail has improved absorption and thus achieves comparable plasma levels at a lower dose, which may reduce side effects and the potential for misuse.

Evzio (hand-held auto-injector for naloxone)
The US FDA approved Evzio, a hand-held auto injector that rapidly delivers a single dose of naloxone to reverse opioid overdose. Evzio can be administered by a family member or caregiver and is small enough to be carried in a pocket.

Updates to Existing Drug Labels

**Pregnancy and Lactation Labeling**
The US FDA published the Pregnancy and Lactation Labeling Rule (PLLR or final rule), which removes the pregnancy letter categories (A, B, C, D, and X) and requires labels to be updated when information becomes outdated.

**Dosing Change for Eszopiclone**
The US FDA reduced the recommended starting dose of eszopiclone from 2 mg/night to 1 mg/night for both men and women. This is because, in some patients, eszopiclone blood levels may be high enough the next morning to cause impairment in activities that require alertness, including driving. In 2013, the FDA issued new dosing requirements for zolpidem due to the risk of next-morning impairment. However, the label change applied only to dosing in women (5 mg IR, 6.25 mg XR).

Influential Research and Clinical Studies

**Inflammation and Mental Illness**
The relationship between inflammation and the risk, course, and treatment of mental illness has been a major research topic this year and will likely continue to be so for some time. Findings that came out in 2014 include:

- Elevated interleukin 6 (IL-6) in childhood linked to increased risk of depression and psychosis in young adulthood\(^1\)
- Elevated C-reactive protein (CRP) during pregnancy associated with increased risk of schizophrenia in offspring\(^2\)
- Elevated proinflammatory cytokines seen in depressed vs. non-depressed individuals, and in obese depressed vs. obese non-depressed individuals\(^3\)
Bipolar Disorder
Researchers have created bipolar stem cells. Using patient-derived induced pluripotent stem cells from bipolar patients, researchers were able to study changes in gene expression as the cells differentiated into neurons. Bipolar disorder neurons had a significantly different transcriptional profile than control neurons, expressing more membrane receptors and ion channel genes. The most notable difference was for transcripts involved in calcium signaling. Pretreatment with lithium altered these effects.4

Schizophrenia
In a multisite, double-blind, randomized trial of patients with schizophrenia or schizoaffective disorder (n=311), there was no statistically significant difference in the rate of efficacy failure for paliperidone palmitate vs. haloperidol decanoate. Efficacy failure was defined as psychiatric hospitalization, the need for crisis stabilization, substantial increase in frequency of outpatient visits, clinician's determination that oral antipsychotic could not be stopped, or clinician's decision to discontinue the long-acting injectable due to lack of efficacy. Weight gain and increase in prolactin occurred significantly more frequently in the paliperidone palmitate group, while akathisia occurred significantly more frequently in the haloperidol decanoate group.5

Posttraumatic Stress Disorder (PTSD)
A study from Walter Reed Army Institute of Research suggests that there is substantial discordance between the revised PTSD criteria in DSM-5 and the criteria in DSM-IV, which may cause legal complications for the numerous veterans seeking benefits and access to care. In the study, 1822 US soldiers were screened using the new PTSD checklist based on DSM-5 criteria (PLC-5) and the original PTSD checklist (PLC-S) based on DSM-IV-TR criteria. The study found the PLC-5 to be equivalent to the PLC-S. However, 30% of soldiers who met DSM-IV-TR criteria did not meet DSM-5 criteria, and 27% of soldiers who met DSM-5 criteria did not meet DSM-IV-TR criteria.6

A proof-of-concept study suggests that ketamine's therapeutic potential may extend to PTSD as well. In a double-blind, randomized, crossover trial comparing ketamine to the active placebo control midazolam, researchers found that ketamine infusion was associated with significant reduction in PTSD symptom severity. The clinical relevance of this study will be subject both to successful replication and to identification of an alternate method of ketamine administration. Methods that are under investigation for depression include intranasal and intramuscular.7

Depression
The idea that combining antidepressants from the outset might reduce time to remission in depression is an intriguing hypothesis, but clinical trial results have been mixed. In a double-blind study, 245 patients with major depressive disorder received either bupropion, escitalopram, or the combination for 12 weeks. Compared to either monotherapy, the combination treatment was not superior in timing of remission or remission rate.8

Alzheimer's Disease
Researchers found that CSF levels of A-beta-42 are associated with Alzheimer's disease, and that this association is independent of APOE genotype. The multinational study included 309 patients with dementia/Alzheimer's disease, 287 patients with prodromal Alzheimer's disease, 399 patients with stable mild cognitive impairment (MCI), and 251 controls. More than 70% of patients in the Alzheimer and prodromal groups carried 1 or 2 copies of the APOE e4 allele. The CSF levels of A-beta-42 were lower in carriers than noncarriers of APOE e4 regardless of diagnosis. However, CSF levels of A-beta-42 differed between participants with Alzheimer's disease compared to controls and to those with MCI, and this was independent of APOE genotype. The researchers therefore conclude that the clinical cutoff for CSF levels of A-beta-42 should be the same for all APOE genotypes.9

Another group of researchers identified a panel of 10 blood proteins that are predictive of Alzheimer onset in people with mild cognitive impairment with nearly 90% accuracy. In the study comparing three cohorts of cognitively healthy elderly, mild cognitive impairment (MCI), and Alzheimer's disease (AD) participants, standardized clinical assessments and neuroimaging were used to identify blood proteins that correlate with disease severity and progression. Of the 26 proteins that were measured, a panel of 10 protein biomarkers was identified as predictive of conversion from MCI to AD within a year of blood sampling. This study validated previously discovered biomarkers associated with AD; however, additional, larger replication is still needed.10
Marijuana Use
In one functional magnetic resonance imaging (fMRI) study, researchers compared the brains of young adult recreational marijuana users (n=20) with those of non-users (n=20). The researchers found that recreational marijuana users had significant alterations in gray matter density and shape of the nucleus accumbens and amygdala; these differences correlated with the frequency and amount of marijuana use. These preliminary data are consistent with animal model studies.11

In another study, researchers measured gray matter volume using structural magnetic resonance imaging in marijuana users (n=48) and non-users (n=62). They found that, compared with controls, marijuana users had significantly less bilateral orbitofrontal cortex (OFC) volume and higher functional connectivity in tracts that innervate the OFC. Higher OFC functional connectivity was associated with earlier age of onset of marijuana use.12

Other Relevant News
- Transition to ICD-10 delayed until October 1, 2015
- CAL-VAT guidelines published for the assessment and treatment of violence and aggression13
- National Collegiate Athletic Association (NCAA) and Department of Defense (DoD) partner to launch a 3-year study of NCAA student athletes14,15
- American Heart Association (AHA) recommends that depression be included as an official heart disease risk factor16
- World Health Organization (WHO) publishes Comprehensive Mental Health Action Plan 2013–202017

Looking Ahead
For ongoing updates in psychopharmacology, NEI Members can access This Month in Psychopharmacology18 on the NEI Web site.

References