

## **PSYCHIATRIC SUMMARY XVII**

**Spring 2016**

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This issue marks the seventeenth installment consolidating recent clinical updates, mental health policy news, popular press news patients may be reading, and changes in the landscape of psychiatry in Wisconsin. Download the full issue.

### **OF GENERAL INTEREST**

#### **SSRIs, Pregnancy and Autism:**

Heavily publicized in the popular press, Boukhris et al (JAMA Pediatrics, [LINK](#)) reported a register-based study of an ongoing population-based cohort using data from 1998 to 2009, including a total of 145,456 singleton live full-term infants with data analysis conducted from October 1, 2014, to June 30, 2015.

They published the following results

During 904 035.50 person-years of follow-up, 1054 children (0.7%) were diagnosed with ASD; boys with ASD outnumbered girls by a ratio of about 4:1. The mean (SD) age of children at the end of follow-up was 6.24 (3.19) years. Adjusting for potential confounders, use of antidepressants during the second and/or third trimester was associated with the risk of ASD (31 exposed infants; adjusted hazard ratio, 1.87; 95% CI, 1.15-3.04). Use of selective serotonin reuptake inhibitors during the second and/or third trimester was significantly associated with an increased risk of ASD (22 exposed infants; adjusted hazard ratio, 2.17; 95% CI, 1.20-3.93). The risk was persistent even after taking into account maternal history of depression (29 exposed infants; adjusted hazard ratio, 1.75; 95% CI, 1.03-2.97).

#### **Prior Authorization for Hospitalization:**

Appearing in The American Journal of Emergency Medicine (Funkenstein et al., [LINK](#)) researchers recorded prior authorization process data for over 200 patients aged 4 to 19 finding an average of nearly 60 minutes required for the physician to obtain prior authorization for hospitalization, ranging from 3 to 270 minutes, extrapolating to an estimated 1.5 million wasted clinician hours per year.

#### **Hours on the EMR:**

Appearing in The Journal of Graduate Medical Education, Chen et al. ([LINK](#)) tracked time spent in the Electronic Medical Record for 41 first year internal medicine residents. They found that the average time spent was 112 hours per month for 206 different encounters, and that chart reviewed dropped from 41 minutes per encounter in July, to around 30 minutes in January and May. Usage time was defined as more than 15 keystrokes or 3 mouse clicks.

### **CLINICAL PSYCHIATRY IN THE NEWS, IN BRIEF**

#### **Pediatric Depression → Brain Changes:**

Using MRI measures of cortical thickness, surface area and volume at three time points, Luby et al. (JAMA Psychiatry) followed 193 children, 90 of whom had a diagnosis of Major Depressive disorder and 116 had 3 waves of scanning. Their results included:

Findings demonstrated marked alterations in cortical gray matter volume loss (slope estimate,  $-0.93 \text{ cm}^3$ ; 95% CI,  $-1.75$  to  $-0.10 \text{ cm}^3$  per scan wave) and thinning (slope estimate,  $-0.0044 \text{ mm}$ ; 95% CI,  $-0.0077$  to  $-0.0012 \text{ mm}$  per scan wave) associated with experiencing an episode of major depressive disorder before the first magnetic resonance imaging scan. In contrast, no

significant associations were found between development of gray matter and family history of depression or experiences of traumatic or stressful life events during this period.

### **Sleep Disruption and Mood:**

In a randomized study of sleep disruptions, including about 20 individuals in each of three groups (forced nocturnal awakenings (FA, n = 21), or one of two control conditions: restricted sleep opportunity (RSO, n = 17) or uninterrupted sleep (US, n = 24), Finan et al. (Sleep, [LINK](#)) measured sleep architecture with polysomnography, and mood, over three consecutive nights. They found that:

Compared to restricted sleep opportunity controls, forced awakenings subjects had significantly less slow wave sleep ( $P < 0.05$ ) after the first night of sleep deprivation, and significantly lower positive mood ( $P < 0.05$ ) after the second night of sleep deprivation. The differential change in slow wave sleep statistically mediated the observed group differences in positive mood ( $P = 0.002$ ).

### **Meta-Analysis of SSRI Dosing:**

In a systematic review and meta-analysis, Jakubovski et al. (Am J Psychiatry, [LINK](#)) explored the balance between higher side effects and higher efficacy of higher doses of SSRIs.

Forty studies involving 10,039 participants were included. Longitudinal modeling (dose-by-time interaction= $0.0007$ , 95% CI= $0.0001-0.0013$ ) and endpoint analysis (meta-regression:  $\beta=0.00053$ , 95% CI= $0.00018-0.00088$ ,  $z=2.98$ ) demonstrated a small but statistically significant positive association between SSRI dose and efficacy. Higher doses of SSRIs were associated with an increased likelihood of dropouts due to side effects (meta-regression:  $\beta=0.00207$ , 95% CI= $0.00071-0.00342$ ,  $z=2.98$ ) and decreased likelihood of all-cause dropout (meta-regression:  $\beta=-0.00093$ , 95% CI= $-0.00165$  to  $-0.00021$ ,  $z=-2.54$ ).

Focusing on efficacy and tolerability, the authors calculated number needed to treat (NNT) and number needed to harm (NNH) and used published dose ranges to convert SSRI doses to imipramine equivalents, with 100 mg of imipramine equivalent to:

- Sertraline, 120 mg
- Fluvoxamine, 100 mg
- Paroxetine, 20 mg
- Fluoxetine, 20 mg
- Citalopram, 33.3 mg
- Escitalopram, 16.7 mg

### **Sleep Fragmentation and Brain Injury:**

Appearing in the journal Stroke, Lim et al. ([LINK](#)) studied sleep fragmentation (based on actigraphy) and severity of arteriolosclerosis, atherosclerosis, and cerebral amyloid angiopathy, and the number of macroscopic and microscopic infarcts in 315 participants of the Rush Memory and Aging Project. Using logistic regression, the authors reported:

Greater sleep fragmentation was associated with more severe arteriolosclerosis (odds ratio, 1.27; 95% confidence interval, 1.02–1.59;  $P=0.03$  per 1 SD greater sleep fragmentation) and more subcortical macroscopic infarcts (odds ratio, 1.31; 95% confidence interval, 1.01–1.68;  $P=0.04$ ). These associations were independent of established cardiovascular risk factors and diseases, and several medical comorbidities

### **Marijuana Use and IQ, Do-Over:**

Another study on the impact of marijuana and IQ was recently published in PNAS (Jackson et al., [LINK](#)) and thoroughly reported in the popular press. Herein, two longitudinal studies of twin pairs were tested

in two windows (ages 9 to 12 before any marijuana exposure and ages 17 to 20, where some had been exposed per self report). The researchers found:

Marijuana users had lower test scores relative to nonusers and showed a significant decline in crystallized intelligence between preadolescence and late adolescence. However, there was no evidence of a dose–response relationship between frequency of use and intelligence quotient (IQ) change. Furthermore, marijuana-using twins failed to show significantly greater IQ decline relative to their abstinent siblings.

### **Depression → Low Back Pain:**

In a study out of the University of Sydney, published in *Arthritis Care and Research* (Pinheiro et al., [LINK](#), News Release [LINK](#)) in which the authors analyzed 11 international studies including 23,109 participants who were not experiencing low back pain, finding that depression (whether clinically diagnosed or self reported) strongly predicted future development of low back pain, with greater severity of depressive symptoms correlating with greater risk for future low back pain.

### **Parent Training Reduces Hyperactivity:**

Exploring the impact of parental training in low-income mother infant dyads, Weisleder et al. (*Pediatrics*, [LINK](#)) showed that promotion of positive parenting through reading aloud and play showed better outcomes than control in imitation/play and attention, separation distress, hyperactivity, and externalizing problems (press release also available [LINK](#)).

### **Concussion as Suicide Risk Factor?**

According to a study published in *CMAJ* (Fralick et al., [LINK](#)) this 20 year longitudinal study of individuals suffering from concussion in Ontario, the authors:

identified 235 110 patients with a concussion. Their mean age was 41 years, 52% were men, and most (86%) lived in an urban location. A total of 667 subsequent suicides occurred over a median follow-up of 9.3 years, equivalent to 31 deaths per 100 000 patients annually or 3 times the population norm. Weekend concussions were associated with a one-third further increased risk of suicide compared with weekday concussions (relative risk 1.36, 95% confidence interval 1.14–1.64). The increased risk applied regardless of patients' demographic characteristics, was independent of past psychiatric conditions, became accentuated with time and exceeded the risk among military personnel. Half of these patients had visited a physician in the last week of life.

### **Lithium vs Valproate vs Quetiapine vs Olanzapine in BPAD:**

A recent study by Hayes et al. appearing in *World Psychiatry* ([LINK](#)) sought to compare rates of monotherapy treatment failure in patients with bipolar disorder prescribed lithium, valproate, olanzapine or quetiapine using a population-based cohort study of 5,089 patients via electronic health records. In this, treatment failure was defined as time to stopping medication or addition of another mood stabilizer, antipsychotic, antidepressant or benzodiazepine. They found that “Lithium appears to be more successful as monotherapy maintenance treatment than valproate, olanzapine or quetiapine. Lithium is often avoided because of its side effect profile, but alternative treatments may reduce the time to being prescribed more than one drug, with potential additive side effects of these treatments.”

### **Benzodiazepines and Dementia Part II:**

In a study appearing in the *BMJ* (Gray et al., [LINK](#)) following nearly 3500 patients 65 years of age or older, the authors found that: “Over a mean follow-up of 7.3 years, 797 participants (23.2%) developed dementia, of whom 637 developed Alzheimer’s disease. For dementia, the adjusted hazard ratios

associated with cumulative benzodiazepine use compared with non-use were 1.25 (95% confidence interval 1.03 to 1.51) for 1-30 TSDDs; 1.31 (1.00 to 1.71) for 31-120 TSDDs; and 1.07 (0.82 to 1.39) for  $\geq 121$  TSDDs. Results were similar for Alzheimer's disease. Higher benzodiazepine use was not associated with more rapid cognitive decline.

#### **Low Exercise and Later Brain Volume Loss:**

Appearing in *Neurology* (Spartano et al., [LINK](#)) authors set out to explore the impact of midlife exercise blood pressure, heart rate, fitness and later brain volume loss in a 20 year longitudinal study of over 1000 subjects. They found that: "Poor CV fitness and greater diastolic BP and HR response to exercise at baseline were associated with a smaller total cerebral brain volume (TCBV) almost 2 decades later (all  $p < 0.05$ ) in multivariable adjusted models; the effect of 1 SD lower fitness was equivalent to approximately 1 additional year of brain aging in individuals free of CVD. In participants with prehypertension or hypertension at baseline, exercise systolic BP was also associated with smaller TCBV ( $p < 0.05$ )."

#### **Paroxetine and Cardiac Malformation:**

In a systematic review appearing in *British Journal of Clinical Pharmacology*, Bérard et al. ([LINK](#)) included twenty-three studies and reported that:

Compared with non-exposure to paroxetine, first trimester use of paroxetine was associated with an increased risk of any major congenital malformations combined (pooled OR 1.23, 95% CI 1.10, 1.38;  $n = 15$  studies), major cardiac malformations (pooled OR 1.28, 95% CI 1.11, 1.47;  $n = 18$  studies), specifically bulbus cordis anomalies and anomalies of cardiac septal closure (pooled OR 1.42, 95% CI 1.07, 1.89;  $n = 8$  studies), atrial septal defects (pooled OR 2.38, 95% CI 1.14, 4.97;  $n = 4$  studies) and right ventricular outflow track defect (pooled OR 2.29, 95% CI 1.06, 4.93;  $n = 4$  studies). Although the estimates varied depending on the comparator group, study design and malformation detection period, a trend towards increased risk was observed.

#### **Opioids for Depression?**

Rehashing a long standing hypothesis, Fava et al (*American Journal of Psychiatry*, [LINK](#)) used a multicenter, randomized, double-blind, placebo-controlled, two-stage sequential parallel comparison design study in adults with major depression who had an inadequate response to one or two courses of antidepressant treatment. They reported improvement in depressive symptom with adjunct treatment using 2mg/2 mg of buprenorphine/samidorphan (the 2/2 dosage group) but not in the 8 mg/8 mg group.

#### **PPIs → Dementia?**

Reported in *JAMA Neurology* and picked up by multiple news sources, Gomm et al., ([LINK](#)) demonstrated a link between use of proton pump inhibitors and subsequent risk for developing dementia. Studying over 73,000 individuals 75 years or older - all free of dementia at baseline, they found that:

The patients receiving regular PPI medication ( $n = 2950$ ; mean [SD] age, 83.8 [5.4] years; 77.9% female) had a significantly increased risk of incident dementia compared with the patients not receiving PPI medication ( $n = 70\ 729$ ; mean [SD] age, 83.0 [5.6] years; 73.6% female) (hazard ratio, 1.44 [95% CI, 1.36-1.52];  $P < .001$ ).

#### **Stimulant Abuse ER Visits Up:**

Appearing in *The Journal of Clinical Psychiatry*, and picked up by multiple news sources, Chen et al., ([LINK](#)) reported:

In adolescents, treatment visits involving dextroamphetamine-amphetamine and methylphenidate decreased over time; nonmedical dextroamphetamine-amphetamine use remained stable, while nonmedical methylphenidate use declined by 54.4% in 6 years. ED visits involving either medication remained stable. In adults, treatment visits involving dextroamphetamine-amphetamine remained unchanged, while nonmedical use went up by 67.1% and ED visits went up by 155.9%. These 3 trends involving methylphenidate remained unchanged. Across age groups, the major source for nonmedical use of both medications was a friend or relative; two-thirds of these friends and relatives had obtained the medication from a physician.

### **Benzodiazepine Overdoses Quadruple:**

Appearing in the American Journal of Public Health, Bachhuber et al., ([LINK](#)) reported that the overdose death rate increased from 0.58 to 3.07 per 100,000 from 1996 to 2013.

### **Flibanserin Meta-Analysis:**

Appearing online ahead of print in JAMA Internal Medicine ([LINK](#)), Jaspers et al. published a systematic review and meta-analysis of 5 published and 3 unpublished studies of Flibanserin for female sexual dysfunction, involving data from 5914 women. They found that “Treatment with flibanserin, on average, resulted in one-half additional SSE [satisfying sexual event] per month while statistically and clinically significantly increasing the risk of dizziness, somnolence, nausea, and fatigue.”

## **MENTAL HEALTH IN THE POPULAR PRESS**

### **Mandated Company Health Screenings or Else?**

Referring to policies at Wisconsin’s plastic manufacturer Flambeau, Bloomberg ran a story (Greenfield, 1/15/2016, [LINK](#)) on how companies are moving from simply charging more for those who don’t get health screenings in wellness programs, to dropping health coverage entirely. According to several courts, including the one that ruled in favor of Flambeau, this is perfectly legal.

### **USPSTF Depression Screening:**

As reported in the 1/27/2016 AMA Morning Rounds, many news sources wrote about new depression screening recommendations:

On its front page, the [New York Times](#) (1/26, A1, Belluck, Subscription Publication) reports that yesterday, the US Preventive Services Task Force (USPSTF) made its first-ever recommendation for “screening for maternal mental illness” in wake “of new evidence that maternal mental illness is more common than previously thought; that many cases of what has been called postpartum depression actually start during pregnancy; and that left untreated, these mood disorders can be detrimental to the well-being of children.” The [guidelines](#) were published online Jan. 26 in the Journal of the American Medical Association.

### **Marijuana Exposure and Verbal Memory in Late Life:**

Appearing in JAMA Internal Medicine, Auer et al. ([LINK](#)) reported on over 5000 black and white men and women enrolled in a longitudinal coronary artery risk study, measuring three cognitive domains: verbal, digit symbol substitution and Stroop interference. Per the results:

Among 3385 participants with cognitive function measurements at the year 25 visit, 2852 (84.3%) reported past marijuana use, but only 392 (11.6%) continued to use marijuana into middle age. Current use of marijuana was associated with worse verbal memory and processing speed; cumulative lifetime exposure was associated with worse performance in all 3 domains of

cognitive function. After excluding current users and adjusting for potential confounders, cumulative lifetime exposure to marijuana remained significantly associated with worse verbal memory. For each 5 years of past exposure, verbal memory was 0.13 standardized units lower (95% CI, -0.24 to -0.02; P = .02), corresponding to a mean of 1 of 2 participants remembering 1 word fewer from a list of 15 words for every 5 years of use. After adjustment, we found no associations with lower executive function (-0.03 [95% CI, -0.12 to 0.07]; P = .56) or processing speed (-0.04 [95% CI, -0.16 to 0.08]; P = .51).

### **Schizophrenia Gene?**

Much was made of the article appearing in Nature (Sekar et al., [LINK](#)) purporting a link between complement component 4 (C4) alleles and synaptic pruning, suggesting this gene may be involved in development of schizophrenia:

Schizophrenia is a heritable brain illness with unknown pathogenic mechanisms. Schizophrenia's strongest genetic association at a population level involves variation in the major histocompatibility complex (MHC) locus, but the genes and molecular mechanisms accounting for this have been challenging to identify. Here we show that this association arises in part from many structurally diverse alleles of the complement component 4 (C4) genes. We found that these alleles generated widely varying levels of C4A and C4B expression in the brain, with each common C4 allele associating with schizophrenia in proportion to its tendency to generate greater expression of C4A. Human C4 protein localized to neuronal synapses, dendrites, axons, and cell bodies. In mice, C4 mediated synapse elimination during postnatal development. These results implicate excessive complement activity in the development of schizophrenia and may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia.

### **Mindful Brain Changes:**

Appearing in both the New York Times (Reynolds 2/18/2016, [LINK](#)) and in Biological Psychiatry (Creswell et al., [LINK](#)) researchers endeavored to create a 'placebo' controlled study of mindfulness meditation for stress reduction, demonstrating that mindfulness training resulted in marked changes in cortical connectivity and reduced IL-6 blood levels.

### **Unlawful Nursing Home Evictions:**

All too familiar to those of us doing hospital based work, AMA Morning Rounds of 2/26/2016 reported: [NPR](#) (2/25, Jaffe) reported in its "Morning Edition" program and on its "Shots" blog that "between 8,000 and 9,000 people complain to the government about nursing home evictions every year," making evictions "the leading category of all nursing home complaints, according to the federal Administration for Community Living." Nursing homes may refuse to readmit residents returning from the hospital if they're on Medicaid, which pays less than Medicare or private insurance. Additionally, patients "who are behaviorally difficult to manage" are more likely to face eviction. In most cases, such evictions are a violation of Federal regulations. Those rules "are rarely enforced by the states," however, so "in California, some nursing home residents are suing the state, hoping to force it to take action."

## **MENTAL HEALTH POLICY**

### **Efficacy of Mental Health Courts?**

In an essay appearing in Kaiser Health News (December 11, 2015; [LINK](#)) Michelle Andrews points out that evidence to their effectiveness is limited and unclear.

### **Call to Lift Ban on Gun Violence Research:**

Multiple medical organizations have called upon congress to lift the federal ban on gun violence research, as reported in the Guardian (Siddiqui, 12/2/2015, [LINK](#)), The Hill (Ferris, 12/10/2015, [LINK](#)).

### **Drug Overdose Deaths Reach Record High in 2014:**

As reported by the National Institutes of Drug Abuse (Revised December 2015, [LINK](#)), drug overdose deaths in the US surpassed 47,000 in 2014, a 7 percent increase from the previous year, the highest amount reported since at least 1970, according to CDC records. The [Washington Post](#) (12/19, Bernstein) pointed out that fatal overdoses due to heroin and prescription pain medications increased by 28 and 16.3 percent, respectively, in 2014, with 10,574 heroin deaths and 18,893 deaths from prescription opioids.

### **Alcohol Related Deaths at 35 Year High:**

Likewise, deaths from alcohol (not including drunk driving and homicides committed under the influence of alcohol) reached a 35 year high in 2014 of 30,700 deaths (CDC Morbidity and Mortality Weekly Report 1/1/2016, [LINK](#)).

### **Benefits of Intensive Care in Schizophrenia:**

Studying over 400 individuals divided into a comprehensive multidisciplinary team based first episode approach and treatment as usual, while more expensive in short term costs, when quality of life scores were factored in, the comprehensive treatment was cost effective (Schizophrenia Bulletin, Rosenheck et al., [LINK](#)).

### **House Democrats Mental Health Reform Bill**

As reported in the AMA Morning Rounds of 2/3/2016:

[The Hill](#) (2/3, Sullivan) reports that yesterday, a group of six House Democrats led by Rep. Gene Green (D-TX) “introduced their own mental health reform bill as they call for changes to a Republican-led measure working its way through the chamber.” In their [bill](#) (pdf), Democrats have cast “aside several of the areas of” Rep. Timothy Murphy’s (R-PA) measure ([HR 2646](#)) to which they have objected. For example, the Democratic bill “does not include financial incentives to states to reward assisted outpatient treatment laws, which allow judges to mandate treatment for patients with serious mental illness.” In addition, it “makes less drastic changes to...HIPAA, which Murphy argues will help give caregivers needed information about the mentally ill but that Democrats have said would hurt patient privacy.”

### **Medicare and Stand-Alone Psychiatric Hospitals:**

Appearing in AMA Morning Rounds of 2/16/2016:

[Modern Healthcare](#) (2/13, Evans, Subscription Publication) reported that in a policy representing “a radical break,” Medicaid “is on the cusp of allowing stand-alone psychiatric hospitals into its provider networks for the first time.” That change, which is anticipated “to be finalized in April, should introduce new capacity and competition in the acute-care psychiatric market.” In addition, it “should increase access to acute mental-health and substance-abuse services for low-income adults.” Writing in support of the proposal, the American Medical Association stated, “While this is not a magic bullet, and does not take the place of more needed investment in community-based treatment resources, it is a step in the right direction.”

### **Black Box Warning for Concurrent Opiates and Benzos?**

According to the 2/23/2016 AMA Morning Rounds:

The [Washington Post](#) (2/22, Dennis) reports in “To Your Health” that “dozens of public health officials and academics across the country are pushing the Food and Drug Administration to warn people about the potential dangers of taking” opioid pain medications along with benzodiazepines. In a petition, officials from 41 state and municipal health departments, as well as some universities, “urged the agency” to add boxed warnings to both medications, “given evidence that using them together increases the chance of deadly overdoses.”