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Research Watch is an initiative by the residents of Case Western Reserve University/University Hospitals Case Medical Center, and it aims to inform psychiatry residents and faculty of notable articles published in prominent research and educational journals.

**Journals Covered:**

- \* American Journal of Psychiatry (AJP)
- \* AJP – Resident’s Journal (RJ)
- \* JAMA Psychiatry (JAMA-P)
- \* Lancet Psychiatry (LP)
- \* Journal of the American Academy of Child & Adolescent Psychiatry (JAACAP)
- \* Current Psychiatry (CP)
- \* International Journal of Psychoanalysis & The American Journal of Psychoanalysis (Psychoanalysis)
- \* Miscellaneous: Nature

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**Highlights**

- Smoking prospectively predicts risk for schizophrenia and demonstrates a clear dose-response relationship (AJP)
- Selective hyperconnectivity between anterior temporal and subgenual cortices, reflective of self-blaming emotions relative to emotions blaming others, is predictive of recurrence of depressive episodes. (JAMA-P)
- Schizophrenia is associated with a more than 2-fold higher risk of all-cause dementia. (JAMA-P)
- Placebo-induced activation of the  $\mu$ -opioid system is implicated in the formation of placebo antidepressant effects in patients with MDD (JAMA-P)
- Baseline depression severity does not moderate differences between CBT and antidepressant medication in response or remission. (JAMA-P)
- PTSD is associated with increased interleukin 6, interleukin 1 $\beta$ , TNF $\alpha$ , and interferon  $\gamma$  levels (LP)
- Experimentally controlled sleep deprivation represents a translational model system given the presence of psychosis-like deficits in translational inhibitory biomarkers—prepulse inhibition and antisaccades—that occur after sleep deprivation. (LP)
- A pilot randomized controlled trial of CBT in adolescents with body dysmorphic disorder showed significant improvement in outcomes at posttreatment and 2 month follow-up. (JAACAP)
- Atomoxetine may be an effective and tolerable medication option for ADHD in individuals with autism spectrum disorder. (JAACAP)
- Induced pluripotent stem-cell model for human bipolar disorder reveals differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. (Nature)

**Research Watch is now accepting submissions of critical commentary pieces by residents & fellows (open to all residency/fellowship programs). See below for details.**

## **Announcement:**

*Research Watch* is now accepting submissions of critical commentary pieces (about 400-500 words; up to 5 references) by residents & fellows (open to all residency/fellowship programs) in which authors can critically discuss recently published studies. Please contact Chief Curator Awais Aftab at [muhammad.aftab@uhhospitals.org](mailto:muhammad.aftab@uhhospitals.org) with submissions. He will serve as editor for these commentary pieces, with Dr Keming Gao (Associate Professor, Psychiatry, CWRU School of Medicine) serving as faculty advisor. Contributions received before 10<sup>th</sup> of the respective month may be considered for publication in that month's issue.

## **The American Journal of Psychiatry**

### **Volume 172, Issue 11**

#### **The Spectrum of Psychiatric Symptoms in Wilson's Disease: Treatment and Prognosis**

Zimbrea PC and Schilsky M

This case report and literature review discusses the psychiatric symptoms and treatment recommendations for Wilson's Disease. Recommendations include therapies to remove and prevent the accumulation of copper along with a slower titration of psychotropic medications. Prognosis for these patient should be a full recovery and patients may maintain remission for years after psychotropic medications have been discontinued, even when there is severe symptomatology initially.

#### **Inflammation: Depression Fans the Flames and Feasts on the Heat**

Kiecolt-Glaser, et al.

This literature review emphasizes the relationship between depression and inflammation and encourages tandem treatment as an option that may enhance recovery and reduce the risk of recurrence. These two entities exacerbate each other as inflammation has been found to contribute to the pathogenesis of a subset of depression while depression is also known to cause larger cytokine responses to stressors and pathogens. Research has found that anti-inflammatory interventions can substantially improve mood in individuals with prolonged inflammatory responses.

#### **Smoking and Schizophrenia in Population Cohorts of Swedish Women and Men: A Prospective Co-Relative Control Study**

Kendler, et al.

This prospective control study used Cox proportional hazard and co-relative control models to predict future risk of schizophrenia and nonaffective psychosis in individuals who smoke. Results showed that

smoking does prospectively predict risk for schizophrenia and demonstrates a clear dose-response relationship. The study also found that in monozygotic twins discordant for smoking, the risk for nonaffective psychosis was appreciably higher in the smoking individual.

**Prospective Longitudinal Evaluation of the Effect of Deployment-Acquired Traumatic Brain Injury on Posttraumatic Stress and Related Disorders: Results from the Army Study to Assess Risk and Resilience in Service members (Army STARRS)**

Stein, et al.

This prospective, longitudinal survey of 4645 soldiers was conducted at different time intervals prior to deployment to Afghanistan and upon re-deployment to the U.S. Surveys found that approximately 1 in 5 soldiers reported exposure to TBIs and deployment-acquired TBIs were associated with elevated odds of PTSD, GAD and MDD, even after adjusting for other risk factors.

**In Vivo Measurement of GABA Transmission in Healthy Subjects and Schizophrenia Patients**

Frankle, et al.

This in vivo study compared 17 off-medication patients with schizophrenia and 22 healthy comparisons and found an impairment in GABA transmission, especially in antipsychotic-naïve individuals and appears to be linked to clinical symptoms.

**The American Journal of Psychiatry - Resident's Journal**

**Volume 10, Issue 11**

**Opioid Prescribing and Iatrogenic Addiction**

Mathis W

Rising mortality from opioid use parallels increased opioid prescribing. A survey of patients seeking treatment for opioid abuse found that 79% of males and 85% of females indicated that their first exposure to opioids was a legitimate prescription for pain. Estimated rates of iatrogenic opioid addiction are small but significant. There are well-characterized risk factors for iatrogenic opioid addiction. These include: patient or family history of substance use disorder, young age, white, male, greater pain experience, pain-related limitations, psychiatric comorbidity, duration of exposure. Physician training (from MD survey, resident survey, and textbook analysis) has not kept pace with opioid prescribing.

**Sexual Sadism Disorder in Forensic Populations**

Johnson, et al

Sexual sadism disorder is most likely to be diagnosed in forensic and correctional settings. Sexual sadists and rapists are not synonymous, as the sadist repeatedly fantasizes about the physical or psychological suffering of others. In order to qualify a sexual sadist for a diagnosis of sexual sadism disorder, the sexually sadistic behavior cannot solely involve consenting individuals willingly submitting to the pain/humiliation.

## **Treatment-Emergent Mania After Initiation of St. John's Wort**

Carp, et al

St. John's wort, a widely available supplement, has long been used as an herbal alternative to treating depression and various mood disorders and has shown similar effect size to selective serotonin reuptake inhibitors. St. John's wort has been reported to be well tolerated but has many drug interactions and may also trigger manic symptoms in some patients. Clinicians must be aware of these issues when advising patients regarding this supplement, especially in light of lax regulation of safety labeling on many widely available St. John's wort products.

## **JAMA Psychiatry**

### **Volume 72, Issue 11**

## **Effect of the Garrett Lee Smith Memorial Suicide Prevention Program on Suicide Attempts Among Youths**

Garraza, et al.

This study looked at community-based suicide prevention programs for youths (16-23 years old) across 26 states and 12 tribal communities, which included comprehensive, multifaceted suicide prevention programs (gatekeeper training, education and mental health awareness programs, screening activities, programs for suicide survivors and crisis hotlines). It showed that suicide rates decreased in counties implementing such programs, with 4.9 fewer attempts per 1000 youths ( $p = .003$ ), though with adults over age 23 there was no difference in suicide rates. This study did not show any difference in long-term suicide attempt rates however.

## **Prevalence of Posttraumatic Stress Disorder in Vietnam-Era Women Veterans - The Health of Vietnam-Era Women's Study (HealthVIEWS)**

Magruder, et al.

A survey of women who were active duty military personnel in the US Armed Forces at any time between 1965-1973 was given out to determine lifetime and current PTSD. Lifetime PTSD in these women was found to be at 20.1% in the Vietnam cohort, 11.5% in the near-Vietnam cohort and 14.1% in the US cohort. Women who served in Vietnam had higher lifetime and current PTSD, however when adjusting for wartime exposures, serving in or near Vietnam did not increase the odds of having current PTSD.

## **Self-blame-Selective Hyperconnectivity Between Anterior Temporal and Subgenual Cortices and Prediction of Recurrent Depressive Episodes**

Lythe, et al.

Patients with remitted MDD were previously found to display abnormal fMRI connectivity between the right superior anterior temporal lobe (RSATL) and the subgenual cingulate cortex and adjacent septal region (SCSR) when experiencing self-blaming emotions relative to emotions blaming others. This study used fMRI in remitted MDD at baseline to test the hypothesis that RSATL-SCSR connectivity for self-blaming relative to other-blaming emotions predicts subsequent recurrence of depressive episodes. It showed that the recurring MDD group showed higher connectivity than the stable MDD group and the control group. Additionally, the recurring MDD group showed RSATL hyperconnectivity with the right ventral putamen and claustrum and the temporoparietal junction. Together these regions predicted recurrence with 75% accuracy.

### **Effects of a Cognitive-Behavioral Prevention Program on Depression 6 Years after Implementation Among At-Risk Adolescents - A Randomized Clinical Trial**

Brent, et al.

This RCT set out to determine whether a cognitive-behavioral program reduced the incidence of depressive episodes, increased depression-free days and improved developmental competence 6 years after implementation in 316 participants aged 13-17 years at enrollment and who had at least one parent with current or prior depressive episodes. The participants themselves could not be in a depressive episode but had to have subsyndromal depression symptoms or a prior depressive episode currently in remission. The cognitive-behavioral program itself consisted of 8 weekly 90-minute group sessions followed by 6 monthly continuation sessions, with a total of 75 months of follow up. The effect of the cognitive-behavioral program was found to be strongest on new onsets of depression and maintained throughout the follow-up period; developmental competence was positively affected 6 years later.

### **Baseline Depression Severity as Moderator of Depression Outcomes Between Cognitive Behavioral Therapy vs Pharmacotherapy - An Individual Patient Data Meta-Analysis**

Weitz, et al.

This systematic literature search showed that baseline depression severity did not moderate differences between CBT and antidepressant medication on the HAM-D or Beck Depression Inventory in response or remission. However, this data cannot be extrapolated to other psychotherapies, individual antidepressants or inpatients.

### **Long Term Risk of Dementia in Persons with Schizophrenia**

Ribe, et al.

In this Danish Population-Based Cohort Study of >2.8 million people (20,683 with schizophrenia): During an 18 year follow-up, schizophrenia was associated with a more than 2-fold higher risk of all-cause dementia after adjusting for age, sex and calendar period.

## **Association Between Placebo-Activated Neural Systems and Antidepressant Responses - Neurochemistry of Placebo Effects in Major Depression**

Pecina, et al.

Study shows that placebo-induced activation of the  $\mu$ -opioid system is implicated in the formation of placebo antidepressant effects in patients with MDD. Additionally, higher baseline  $\mu$ -opioid receptor binding in the nucleus accumbens is associated with a better response to antidepressant treatment. There were reductions in depressive symptoms after 1 week of active placebo treatment, compared with inactive placebo (inactive meaning that patients were told they were being given an inactive control), which were associated with increased placebo-induced  $\mu$ -opioid neurotransmission in a network of regions implicated in emotion, stress regulation and the pathophysiology of MDD. These regions included the subgenual anterior cingulate cortex, nucleus accumbens, midline thalamus, and amygdala. Placebo-induced endogenous opioid release in these regions was associated with better antidepressant treatment response, predicting 43% of the variance in symptom improvement at the end of the antidepressant trial.

## **Cortical Representation of Afferent Bodily Signals in Borderline Personality Disorder - Neural Correlates and Relationship to Emotional Dysregulation**

Muller, et al.

Heartbeat evoked potentials (HEPs) are an indicator of the cortical representation of afferent signals from the cardiovascular system. In this study mean HEP amplitudes in resting-state EEG and their correlation with self-reported emotional dysregulation and gray matter volume was measured in patients with borderline personality disorder (BPD). Patients with BPD had significantly reduced mean HEP amplitudes compared with healthy volunteers, whereas the mean HEP amplitudes of patients with BPD in remission lie somewhere in between these 2 groups of participants. The HEP amplitudes were negatively correlated with emotional dysregulation and positively associated with gray matter volume in the left anterior insula and the bilateral dorsal anterior cingulate cortex, 2 structures that have been identified as core regions for interoception.

## **The Lancet Psychiatry**

### **Volume 2, Issue 11**

#### **Efficacy of CBT for sleep improvement in patients with persistent delusions and hallucinations (BEST); a prospective, assessor-blind, random controlled pilot trial**

Freeman, et al.

This prospective, assessor-blind, randomised controlled pilot trial (Better Sleep Trial [BEST]) assessed CBT for treatment of insomnia in patients with persistent distressing delusions or hallucinations. Compared with standard care, CBT led to reductions in insomnia in the large effect size range at week 12 (adjusted mean difference 6.1, 95% CI 3.0–9.2, effect size  $d=1.9$ ). By week 12, nine (41%) of 22 patients receiving CBT + standard care, and one (4%) of 25 patients receiving standard care alone no longer had insomnia.

### **Interventions to reduce suicide at suicide hotspots: a systemic review and meta-analysis**

Pirkis, et al.

Various interventions have been introduced to try to prevent suicides at suicide hotspots. This systematic review and meta-analysis reveals that interventions that restricted access to means were associated with a reduction in the number of suicides per year, as were interventions that encourage help-seeking, and interventions that increase the likelihood of intervention by a third party.

### **Inflammatory markers in Post-Traumatic Stress Disorder: A systemic review, meta-analysis and meta-regression**

Cavalcante, et al.

This systematic review, meta-analysis, and meta-regression reveals that PTSD is associated with increased interleukin 6, interleukin 1 $\beta$ , TNF $\alpha$ , and interferon  $\gamma$  levels. This information might be useful for consideration of chronic low-grade inflammation as a potential target or biomarker in PTSD treatment.

### **Identifying the lost generation of adults with Autism Spectrum conditions**

Lai, et al.

The review discusses how first diagnosis of autism in adulthood has finally become recognised as an important clinical issue due to the increasing awareness of autism, broadening of diagnostic criteria, and the introduction of the spectrum concept. Making a first diagnosis of autism spectrum conditions in adults can be challenging for practical reasons (eg, no person to provide a developmental history), developmental reasons (eg, the acquisition of learnt or camouflaging strategies), and clinical reasons (eg, high frequency of co-occurring disorders). In delineating differential diagnoses, true comorbidities, and overlapping behaviour with other psychiatric diagnoses, particular attention should be paid to anxiety, depression, obsessive-compulsive disorder, psychosis, personality disorders, and other neurodevelopmental disorders. Possible misdiagnosis, especially in women, should be explored.

### **Effects of sleep deprivation on inhibitory biomarkers of schizophrenia: implications for drug development**

Ettinger, et al.

Authors argue that experimentally controlled sleep deprivation represents a translational model system that can be studied in combination with neurocognitive biomarkers. They review data on the psychotomimetic effects of sleep deprivation in healthy human beings and provide evidence of the psychosis-like deficits in translational inhibitory biomarkers—prepulse inhibition and antisaccades—that occur after sleep deprivation.

**Journal of the American Academy of Child and Adolescent Psychiatry**  
**Volume 54, Issue 11**

**Randomized Clinical Trial of Family-Based Treatment and Cognitive Behavioral Therapy for Adolescent Bulimia Nervosa**

LeGrange, et al

The objective of this study was to compare the efficacy of cognitive-behavioral therapy and family-based treatment for adolescent bulimia nervosa. This 2-site study was a randomized controlled trial that included 130 participants (aged 12-18 years) meeting DSM-IV criteria for BN or partial BN. Treatments involved 18 outpatient sessions over 6 months and outcomes were assessed at baseline, end of treatment, and 6 and 12 months posttreatment. Primary outcome was abstinence from binge eating and purging for 4 weeks before assessment. Results showed that study participants who received family-based treatment achieved higher abstinence rates than those who received cognitive-behavioral therapy at the end of treatment and at 6-month follow up. However, by the 12-month follow up, there were no statistically significant differences between the two treatments.

**A Pilot Randomized Controlled Trial of Cognitive Behavioral Therapy for Adolescents with Body Dysmorphic Disorder**

Mataix-Cols, et al

This pilot randomized controlled trial evaluated the efficacy of an age-appropriate cognitive behavioral therapy (CBT) protocol for adolescents with Body Dysmorphic Disorder (BDD). The study included thirty adolescents between the ages of 12-18 with a primary diagnosis of BDD along with their families who were randomly assigned to either 14 sessions of CBT over 4 months or a control condition consisting of written psycho-education materials and weekly telephone monitoring. Participants were assessed at baseline, midtreatment, post-treatment, and at 2 month follow-up with the primary outcome measure being the Yale-Brown Obsessive-Compulsive Scale Modified for BDD, Adolescent Version. The CBT group showed a significantly greater improvement than the control group, both at posttreatment and at 2-month follow-up. Participants also reported improvement on secondary outcomes including insight, depression, and quality of life at posttreatment.

**Atomoxetine, Parent Training, and Their Combination in Children with Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder**

Harden, et al

This study examined individual and combined-effectiveness of atomoxetine and parent training (PT) for ADHD symptoms and noncompliance. It was a 3-site, 10 –week double-blind, trial of Atomoxetine and PT including 128 children between the ages of 5-14 years with autism spectrum disorder and ADHD. Patients were randomized to atomoxetine, atomoxetine with parent training, placebo with parent training, or placebo. Nine parent-training sessions were provided. The study's primary outcomes

measures were the parent-rated DSM ADHD symptoms on the Swanson, Nolan, and Pelham scale and Home Situations Questionnaire. Results indicated that the atomoxetine group, atomoxetine with parent training group, and placebo with parent training group were each superior to placebo. Atomoxetine and atomoxetine with parent training groups were associated with significant decreases on measures of noncompliance, suggesting that it may have a better side effect profile than psychostimulants in the population with autism spectrum disorder.

### **A Randomized, Placebo-Controlled Trial of Guanfacine Extended Release in Adolescents with Attention-Deficit/Hyperactivity Disorder**

Wilens, et al

This was a phase 3 trial that assessed the safety and efficacy of guanfacine extended release in adolescents with ADHD. It was a 13-week, multicenter, randomized, double-blind, placebo-controlled trial that evaluated once-daily guanfacine extended release in adolescents with ADHD ages 13-17 years. The primary endpoint was the change from baseline in the ADHD Rating-Scale- IV total score. The study included a total of 314 participants who were randomized to guanfacine extended release and placebo. Approximately 47% of participants received an optimal dose above the currently approved maximum dose limit of 4 mg. Participants receiving guanfacine extended release showed statistically significant improvement in the ADHD-RS-IV total score compared with placebo.

### **Correlates and Consequences of Suicidal Cognitions and Behaviors in Children Ages 3 to 7 years**

Whalen, et al

This study was designed to identify trajectories of suicidal ideation across childhood. It was a study consisting of 306 participants who were enrolled in a prospective longitudinal investigation of young children and their families. A baseline assessment was completed by children and their families between ages of 3 and 7 years and at least 1 follow-up assessment between the age of 7-12. Child psychopathology, suicidal thoughts, plans, and behaviors were assessed via parent and trained interview prior to the age of 9 and with self-report after the age of 9. Maternal history of psychopathology, as well as maternal and family history of suicide attempts were also obtained. Results indicated that early-childhood SI (defined as suicidal thoughts, behavior, or any expression of plans/attempts occurring prior to the age of 7) and suicidal themes in play were associated with childhood attention deficit hyperactivity disorder and oppositional defiant/conduct disorders. Early –childhood SI was a risk factor for continuation into school-age SI.

## **Current Psychiatry**

### **Volume 14, Issue 11**

#### **Botulinum Toxin for depression? An idea that's raising some eyebrows**

Magid & Reichenberg

Working under the assumption that there is a paradigm shift in depression (from norepinephrine and serotonin to inflammation, genetics, methylation and neuroplasticity), a dermatologist reported a case series of 10 depressed patients in 2006 who reported improved depressive symptoms after two months following treatment with botulinum toxin A (BTA) in the forehead. The authors conducted a RCT in which patients with depression received injections of BTA in the glabellar region of the forehead, the muscles which contract during expressions of fear, anger, sadness or anguish. Patients noted improvement in depressive symptoms as early as 2 weeks and the effect lasted from 4-6 months at which time repeat BTA injections were recommended for maintenance. Theories include the facial feedback hypothesis, improved social interactions due to more pleasant facial expressions, and both direct and indirect neurochemical changes in the brain. Based on the author's clinical experience and review of literature, BTA appears to be affective for monotherapy and augmentation for treatment of depression, however, it is not FDA approved for treatment of depression at this time.

### **An under-recognized epidemic of elder abuse needs your awareness and action**

Hubert & Gupta

Studies suggest that as many as 10% of older adults in the US experience elder abuse each year. A 2000 APS survey, indicated that 60.7% of abuse occurs in domestic settings and only 8.3% in institutions. Of the 5 categories of abuse, the prevalence of neglect is highest at 58.7% followed by physical, financial, psychological/emotional and sexual. Physical abuse is most common in nursing home settings, especially resident on resident abuse complicated by cognitive decline. In the past, financial abuse was more commonly seen with adult children, however, in more recent years, it is more likely to be a spouse. Risk factors include: female gender, lower income, poor health, lower social support, and belonging to a non-Caucasian racial group. Mental illness, especially dementia, and sexual orientation also put elders at an increased risk for abuse. Male caregivers >40 years, caregivers with fatigue, medical illness, mental illness, lack of financial support, history of abusive behavior and substance use are at an increased risk for committing elder abuse. This article goes into greater detail on assessing if physical signs are indicative of abuse, screening questions, and how to report concern for abuse.

### **Venlafaxine discontinuation syndrome: Prevention and management**

Aftab A (Case/UH resident PGY2)

Venlafaxine has a half-life of 3 to 7 hours which increases the risk of discontinuation syndrome when compared to antidepressants with a longer half-life. Additionally, the frequency of discontinuation symptoms are increased with higher dosages of venlafaxine and longer duration of treatment. The discontinuation symptoms include flu-like symptoms, headache, dizziness, vertigo, sensory disturbances, agitation, anxiety, insomnia, and nightmares; symptoms are not affected by immediate release versus extended release formulations. It is recommended that Venlafaxine be tapered at least at a dose reduction of 75mg per day at 1 week intervals; immediate switching or cross taper to SSRI or SNRI is not recommended, although SSRIs with longer half-lives, such as fluoxetine, can help alleviate some discontinuation symptoms.

## **International Journal of Psychoanalysis**

### **Volume 96, Issue 5**

#### **Delusion and bi-ocular vision**

Masi FD

De Masi observes that delusions represent, “A grave disjunction in the psyche whose outcome is not readily predictable.” Exploring this assertion in the context of clinical work, he considers potential for transformation within analysis.

#### **Psychotic Functioning in Adolescence: The Perverse Solution to Survive**

Nicolò AM

Anna Maria Nicolò examines emergent psychotic experience in adolescence and subsequent defensive responses. With particular attention to perverse defenses, Nicolò considers how to differentiate perverse defense perverse character structure.

## **The American Journal of Psychoanalysis**

### **Volume 75, Issue 3**

#### **Giving birth in exile: motherhood as reterritorialization**

Pestre E

Dr. Pestre explores the effects of exile on subjective experiences in the peripartum period through the lens of deterritorialization and reterritorialization processes. In light of her observations, she considers evaluation and treatment in pregnancies which are often marked by pain and difficulty.

## **Miscellaneous**

#### **Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder**

Mertens, et al.

*(Case/UH faculty Dr Joseph Calabrese is among the authors.)*

Nature 527, 95–99 (05 November 2015) doi:10.1038/nature15526

The introduction of induced pluripotent stem-cell (iPSC) technology has provided a new approach for developing biological models for bipolar disorder. Mertens et al. developed an iPSC model for human bipolar disorder and investigated the cellular phenotypes of hippocampal dentate gyrus-like neurons derived from iPSCs of patients with bipolar disorder. Mitochondrial abnormalities in young neurons from patients with bipolar disorder were detected by using mitochondrial assays; in addition, hyperactive

action-potential firing was observed. This hyperexcitability phenotype of young neurons in bipolar disorder was selectively reversed by lithium treatment only in neurons derived from patients who also responded to lithium treatment. Therefore, hyperexcitability is one early endophenotype of bipolar disorder, and the model of iPSCs in this disease might be useful in developing new therapies and drugs aimed at its clinical treatment.