PANDAS

Among novel concepts in psychiatry, evidence is growing that infections and the immunological response to them might play a role in causing mental disorders. Childhood obsessive-compulsive disorder (OCD) and tic disorders may be associated with infections caused by group A beta-hemolytic Streptococcus. A syndrome has been named based on this hypothesis—pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). Theoretically, antibodies against streptococci cross-react with the basal ganglia because of structural similarities, leading to neuropathological changes and behavioral symptoms. Findings of autoantibodies against the basal ganglia in serum from children with PANDAS, as well as focal brain inflammation, support the concept of this syndrome. Children with PANDAS have been found to have exacerbations in OCD and tics after streptococcal infections, and immunotherapy has shown benefits. However, not all studies have yielded positive results, and many have methodologic limitations. In the largest study of PANDAS to date, Orlovska and others used nationwide registers in Denmark to conduct population-based cohort research.

The population observed was over 1 million subjects younger than 18 years. More than 600,000 received a streptococcal test, and in 55%, at least one test was positive. Boys and girls with a positive strep test had an 18% increased risk of any mental disorder, a 51% increased risk of OCD, and a 35% increased risk of tic disorder—all to statistically significant degrees. Participants with a nonstreptococcal throat infection also had an increased risk of any mental disorder, but streptococcal infections were associated with greater risks.

This large and carefully conducted study opens new vistas for further research and understanding of psychiatric and brain disorders. Doctors have long understood the association of streptococcal infections in youth with cardiac and renal malfunction. Knowing that brain integrity also may be vulnerable to these infections points to potential prevention strategies, such as immunotherapies, which merit further exploration for PANDAS and perhaps other neuropsychiatric disorders. Experts have recently issued comprehensive treatment recommendations for PANDAS. Of course, the first-order prevention strategy is to treat streptococcal infections, like pharyngitis, early and vigorously.


MORTALITY IN SCHIZOPHRENIA: DO ANTIPSYCHOTICS INCREASE THE RISK?

Adults with schizophrenia have a mortality rate even higher than that of other psychiatric patients. On average, their life expectancy is 20 to 25 years shorter than that of the general population. We have often noted that a major contributor to this increased mortality is cardiovascular disease. People with schizophrenia tend to eat poorly and exercise infrequently. Thus, they are often overweight. Compounding these factors, patients with chronic mental illnesses often have poor access to health care and are reluctant to use it.

Do antipsychotic agents also contribute to premature mortality in schizophrenia? Undoubtedly, many antipsychotics worsen cardiovascular risk factors—such as weight gain, diabetes mellitus, and dyslipidemia—and thereby contribute to mortality (BTP 2017;40:33). But it remains unclear whether exposure to these drugs shortens life expectancy in people with schizophrenia. In the Netherlands, Vermeulen and collaborators conducted a systematic review and meta-analysis of studies on mortality and antipsychotic medication in adults with schizophrenia.

Twenty studies met the reviewers’ inclusion criteria. In all, there were 23,353 deaths among 133,929 patients. Compared with patients who had no antipsychotic drug exposure, patients...
who had taken medication had a lower long-term mortality risk. Based on four large cohort studies of moderate to high quality, the pooled risk with antipsychotic exposure was 0.57 ($P < .001$).

Current literature leaves many unanswered questions on this vital subject. Most studies lacked adequate measurement of cumulative drug exposure, and data on common causes of death were often missing. Vermeulen et al hypothesize that patients with schizophrenia who have never taken antipsychotic medication represent a severely ill group. Presumably, they have poor insight and receive little help from either mental health or general health providers.

The most important take-away message from this well-designed review is the need for further study and understanding of health and illness among people with schizophrenia, including optimization of antipsychotic intervention. It is reassuring that antipsychotic drugs do not increase mortality risk and, in fact, appear to reduce it. The findings from this paper reinforce the need for a team-based approach to patients with chronic mental illness—a team that includes psychiatrists and other healthcare providers, along with dieticians and recreational specialists. It is vital to engage patients and, where possible, family members to construct a long-term care plan that incorporates behavioral components, dietary counseling, a physical activity program, and thoughtful pharmacologic and medical intervention and monitoring.


LITHIUM RISKS IN PREGNANCY

In the 1970s, emerging data suggested that lithium use early in pregnancy increased the risk of Ebstein anomaly, a right ventricular outflow tract obstruction, by as much as 400-fold. The risk of cardiac defects overall appeared to increase by a factor of five. Most subsequent evidence on the risks of lithium to the developing fetus comes from case reports and small studies, and data are conflicting. With funding from the United States National Institute of Mental Health, Patorno and colleagues designed a large, retrospective cohort study of pregnant women enrolled in Medicaid.


SUVOREXANT (BELSOMRA) TO PREVENT DELIRIUM?

Orexin neurons help the brain maintain wakefulness and then fall silent during sleep. Decreased orexin signaling might underlie narcolepsy. Since antiquity, people have sought nostrums to promote sleep, and drugs that block orexin neuropeptides from binding to their receptors have been explored as hypnotics. In 2014, the US FDA approved suvorexant (Belsomra), an orexin-1 and orexin-2 antagonist, to treat sleep-onset and/or sleep-maintenance insomnia (BTP 2015;38:27-28).

Suvorexant may also be beneficial in treating delirium. Delirium is a common and deadly alteration in consciousness characterized by an abrupt deterioration in attention, awareness, and cognition. It is more common in older patients and frequently seen postoperatively and in intensive care units. Management consists of searching for correctible underlying causes (eg, fluid and electrolyte disturbances, infection) and supporting vital functions. There is no standard antidote. Based on abnormalities in the sleep-wake cycle that are common in delirium and their own clinical observations of patients at risk for delirium who were treated with suvorexant for insomnia, Hatta and collaborators decided to study the use of suvorexant to prevent delirium.

With funding from the Japan Society for the Promotion of Science, investigators conducted a rater-blinded, parallel-group, randomized, placebo-controlled trial in four Japanese hospitals. Patients, 65 to 89 years old and newly admitted because of emergencies, received suvorexant, 15 mg ($N = 36$), or placebo ($N = 36$) each night for 3 days.

Six (17%) of the patients who received placebo but none of those who took suvorexant developed delirium in the hospital ($P = .025$). There were no significant differences in adverse effects, nor were there differences between treatment groups in sleep metrics.

Delirium is common in hospitals, hospices, and other acute care settings, especially among elderly patients. It often predicts imminent demise. Good medical treatment, careful monitoring, and attention to early infection and pharmacologic interactions can sometimes prevent delirium. Because there is no clear-cut antidote, the study by Dr Hatta’s group is encouraging and warrants attempts at replication.

BIPOLAR DEPRESSION: ONGOING SEARCH FOR NEW AVENUES

In the lifetime course of bipolar disorder, mania and hypomania are more likely than depression to come to family, clinical, and societal attention. But depressive episodes and subsyndromal depressive symptoms usually dominate the course of the illness and are more likely to predict functional outcomes and premature mortality. Unfortunately, today’s treatments are limited. FDA-approved medications for the acute treatment of bipolar depression are the olanzapine-fluoxetine combination.

The authors tracked 1,325,563 pregnancies that resulted in a live birth between 2000 and 2010. Cardiac malformations were compared between infants exposed to lithium in the first trimester and unexposed infants. A secondary analysis also examined babies born to women who had taken lamotrigine (Lamictal and others).

Cardiac malformations occurred in 16 (2.41%) of 663 infants exposed to lithium, in 27 (1.39%) of 1945 infants exposed to lamotrigine, and in 15,251 (1.15%) of 1,322,955 unexposed infants. The adjusted risk ratio for lithium exposure was 1.65. Of particular interest was a clear dose-risk relationship. When the daily lithium dose was 600 mg or less, the risk ratio was only 1.11. For a daily dose between 601 and 900 mg, the risk ratio climbed to 1.60, and at doses above 900 mg/day, it was 3.22. The overall presence of right ventricular outflow tract obstruction was 0.6% in lithium-exposed infants versus merely 0.18% among unexposed offspring. Lithium was not significantly associated with noncardiac malformations.

The authors conclude that lithium use during the first trimester of pregnancy—especially at higher daily doses—can raise the chances of cardiac malformations in babies, but the risk is much lower than previously believed: approximately 1 additional case per 100 live births. But other mood stabilizers, such as valproate (Depakote and others), are also teratogenic, and unchecked mood fluctuations in a woman with bipolar disorder can be hazardous for mother, family, and the developing fetus. Therefore, the best overall strategy is to weigh relative risks against potential benefits, and for the treatment team to discuss options with the woman and, ideally, her partner.

Available treatments for social function impairments in schizophrenia are limited. Because the hypothalamic peptide oxytocin has been found to have diverse prosocial effects in healthy volunteers and people with autism, it is one of the novel pharmacological options being considered for this indication. Jarskog and colleagues investigated whether 12 weeks of treatment with intranasal oxytocin would improve social cognitive function in outpatients with schizophrenia or schizoaffective disorder (Schizophr Res 2017;185:88-95). In this double-blind study, 68 subjects were randomized to oxytocin, 24 IU bid, or placebo. Social cognitive function was assessed at baseline, 6 weeks, and 12 weeks. In addition, psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS). The study found no significant advantages for oxytocin over placebo on social cognition. Primary outcomes of emotion perception, theory of mind, and attributional style did not show a differential advantage of oxytocin compared with placebo. However, oxytocin did show a significant within-group reduction in PANSS negative symptoms and significant between-group improvement in negative symptoms in the schizophrenia subgroup. The authors conclude that further research is needed on the therapeutic potential of oxytocin for social cognitive deficits, social function, and negative symptoms in people with schizophrenia. One area to investigate further is whether lower or higher doses may provide benefits in longer-term studies.

IN BRIEF

- Available treatments for social function impairments in schizophrenia are limited. Because the hypothalamic peptide oxytocin has been found to have diverse prosocial effects in healthy volunteers and people with autism, it is one of the novel pharmacological options being considered for this indication. Jarskog and colleagues investigated whether 12 weeks of treatment with intranasal oxytocin would improve social cognitive function in outpatients with schizophrenia or schizoaffective disorder (Schizophr Res 2017;185:88-95). In this double-blind study, 68 subjects were randomized to oxytocin, 24 IU bid, or placebo. Social cognitive function was assessed at baseline, 6 weeks, and 12 weeks. In addition, psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS). The study found no significant advantages for oxytocin over placebo on social cognition. Primary outcomes of emotion perception, theory of mind, and attributional style did not show a differential advantage of oxytocin compared with placebo. However, oxytocin did show a significant within-group reduction in PANSS negative symptoms and significant between-group improvement in negative symptoms in the schizophrenia subgroup. The authors conclude that further research is needed on the therapeutic potential of oxytocin for social cognitive deficits, social function, and negative symptoms in people with schizophrenia. One area to investigate further is whether lower or higher doses may provide benefits in longer-term studies.

- A new analysis released by the Centers for Disease Control and Prevention reports that the rate of suicide among teenaged girls in the United States doubled between 2007 and 2015 and is the highest it has been in 40 years (Fox M. NBC News website. August 3, 2017. Available at: https://www.nbcnews.com/health/health-news/suicides-teen-girls-hit-40-year-high-n789351). Overall suicide rates have increased 28% since 2000. Suicide rates for males aged 15 to 19 years increased from 12 to 18 per 100,000 between 1975 and 1990. Rates fell between 1990 and 2007, and then started to rise again, up to 14 per 100,000 teenaged boys by 2015. Although suicide rates were lower for females aged 15 to 19 years than for similarly aged males from 1975 to 2007, they followed the same pattern. In 2007, 4320 people aged 24 years or younger died by suicide. In 2015, that number was 5900. Causes of this increase are postulated to include the economic recession in 2008 (financial stresses experienced by parents can affect vulnerable youth) and exposure to violence, such as child abuse and neglect, bullying, and sexual violence. Social media can have both positive and negative effects: it can help reduce suicide by spreading information about signs of suicide risk and how to get help, but it can be detrimental by allowing cyberbullying, and by spreading myths about or glamorizing suicide. Every day, on average, 16 youths in the United States die by suicide.

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combination (Symbyax), quetiapine (Seroquel and others), and lurasidone (Latuda). Because prominent features of bipolar depression include fatigue, hypersomnia, psychomotor inhibition, and concentration difficulties, Szmulewicz and others reviewed dopaminergic agents for its treatment.1

The authors conducted a systematic review and meta-analysis of randomized controlled trials of modafinil (Provigil and others), armodafinil (Nuvigil), pramipexole (Mirapex), methylphenidate (Ritalin and others), and two amphetamines as adjunctive treatments for patients with bipolar depression. They identified nine studies that included 1716 patients. Compared with either an active medication or placebo, the dopaminergic drugs improved response by 25% and remission by 40%. There was no apparent increase in the risk of mood switching.

The reviewers point out common adverse effects of the medications studied. Modafinil and armodafinil are usually well tolerated but may cause headaches, palpitations, and irritability. Amphetamines and methylphenidate have been associated with headache, palpitations, insomnia, and tremor. Side effects with pramipexole have included nausea, pathological gambling, and impulsivity.

Szmulewicz et al caution that most of the trials in their review were short-term. Nonetheless, they believe further research in this area should be pursued and that adjunctive dopamine-enhancing agents merit a role in treatment algorithms for bipolar depression.

A negative trial in bipolar depression recently emerged from the National Institute of Mental Health Intramural Research Program. Park and collaborators were pursuing promising research on intravenous ketamine for the treatment of depression and assessing other glutamatergic modulators, such as riluzole (Rilutek), an oral agent approved by the FDA to delay the neurodegeneration of amyotrophic lateral sclerosis.2

In a randomized, double-blind, placebo-controlled trial, researchers recruited subjects with bipolar disorder who were 18 to 70 years old and in a current episode of depression. After other medications were tapered and discontinued, patients were randomly assigned to receive riluzole, 50 to 200 mg/day, or placebo for 8 weeks. When no significant differences in depressive symptoms were observed between groups in an initial 19 subjects, and no subject had achieved response, the study was discontinued prematurely, and no additional subjects were recruited.

Safe and effective treatment for depressive symptoms and episodes in people with bipolar disorder remains an unmet clinical need. The next breakthrough might come from dopaminergic agents, glutamatergic compounds, or a novel direction. Perhaps the microbiome will emerge as a treatment target. In addition to the few FDA-approved drugs for this indication, clinicians might consider careful use of off-label dopaminergic medication as adjuncts. In most cases, targeted individual and family psychotherapy can enhance clinical stability and amplify medication effects.


COMING SOON:

Can Lithium Decrease the Risk of Dementia?  
Generic vs Brand-Name Antipsychotics  
Gabapentinoids: Are They Overprescribed for Pain?