Advances in ADHD Management

Also in This Issue

Reviewing the Treatment Landscape for the Management of ADHD

Discrepancies Between Men and Women Show Up in ADHD Prescriptions

Samuele Cortese, MD, PhD: The Current State of ADHD Treatment

David W. Goodman, MD: New Treatments Coming for ADHD
CONTENTS

5 Data Reveal Disparities in Mental Health Treatments Among Pediatric Populations

15 Discrepancies Between Men and Women Show Up in ADHD Prescriptions

16 ADHD and Autism Are Associated With Increased Hospital Stays in Early Childhood

17 PCOS Increases Risk of Psychiatric, Neurodevelopment Disorders in Offspring

19 Investigators Find Link Between ADHD and Sleep Issues in Adolescents

20 Featured Peer Exchange - “Treatment Landscape for the Management of ADHD”

22 Maternal Hypertension Raises Risk of Mental Health Disorders in Children

24 Findings Connect Prenatal Acetaminophen Exposure With Higher ADHD Risk

26 Endocrine-Disrupting Chemicals May Play Part in ADHD-Related Behaviors

28 Interactive News

CONNECT WITH US
Data Reveal Disparities in Mental Health Treatments Among Pediatric Populations

By Jonathan Alicea

In 2016, about 16.5% of US children had received a diagnosis of a mental health disorder. Among the most common diagnoses were attention-deficit/hyperactivity disorder, anxiety, and behavioral disorders.

A new data brief from the National Center for Health Statistics (NCHS) reports on 2019 trends in mental health treatment among children aged 5 to 17 years. The investigators uncovered 4 major findings in their analysis, underscoring associations between treatment likelihood and key demographic characteristics such as age, sex, race/ethnicity, and urbanization level of residence.

Benjamin Zablotsky, PhD, and Emily Terlizzi, MPH, of the NCHS, used data from the 2019 National Health Interview Survey, a nationally representative household survey of the US population, to determine the prevalence of mental health treatments among school-aged children.

They found that 13.6% of the prespecified population had received treatment in the past 12 months. Furthermore, 10.0% of children had received counseling or therapy from a mental health professional, and 8.4% had taken prescription medication for their mental health.

Additionally, the investigators’ analysis showed that the prevalence of treatment was greater in older children, aged 12 to 17 years, compared with those aged 5 to 11 years (16.8% vs 10.8%, respectively).

The older children were also more likely to have taken medication for their mental health (10.9% vs 6.2%, respectively) and to have received counseling or therapy from a mental health professional (12.5% vs 7.8%, respectively) in the same time period.

The report also indicated that 14.8% of boys received any mental health treatment compared with 12.4% of girls. Boys (9.8%) were more likely than girls (7.0%) to have been treated with medication, but there was no significant difference in use of counseling by a health care professional.

In terms of race/ethnicity, more non-Hispanic White children (17.7%) had received any mental health treatment compared with Hispanic (9.2%) and non-Hispanic Black (8.7%) children.

This trend was also consistent in use of medication and reception of counseling or therapy. Non-Hispanic White children were more than twice as likely (11.4%) to have taken medication for a mental health disorder as Hispanic (4.7%) and non-Hispanic Black (5.6%) children.

Finally, the investigators found that the percentage of children receiving any mental health treatment increased as urbanization decreased. For example, 12.4% of children in large metropolitan areas received treatment compared with 17.0% in nonmetropolitan areas.

This trend was similar in terms of medication use: 7.4% in large metropolitan areas vs 11.8% in nonmetropolitan areas. There was no observed significant difference in receipt of counseling or therapy.

Zablotsky and Terlizzi said that several of these findings, most notably in the domains of race/ethnicity and level of urbanization, were consistent with prior studies on prescription medication or counseling usage among children.

REFERENCE
Missing doses of oral antipsychotics can cause repeated relapse. With each relapse comes the risk of losing the progress that you have made together.

See the safety and efficacy results of a study where INVEGA SUSTENNA® significantly delayed time to relapse vs commonly prescribed oral antipsychotics.

To view the data, simply scan this QR code or visit InvegaSustennaHCP.com

INDICATION
INVEGA SUSTENNA® (paliperidone palmitate) is indicated for the treatment of:

- Schizophrenia in adults.

IMPORTANT SAFETY INFORMATION FOR INVEGA SUSTENNA® (paliperidone palmitate)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.
See full Prescribing Information for complete Boxed Warning.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA SUSTENNA® is not approved for use in patients with dementia-related psychosis.

Please see additional Important Safety Information and Brief Summary of the full Prescribing Information for INVEGA SUSTENNA® on following pages of this advertisement.

Actor Portrayal
IMPORTANT SAFETY INFORMATION (cont’d)

Contraindications: INVEGA SUSTENNA® is contraindicated in patients with a known hypersensitivity to either paliperidone, risperidone, or to any excipients of the INVEGA SUSTENNA® formulation.

Cerebrovascular Adverse Reactions: Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attacks), including fatalities, were reported at a higher incidence in elderly patients with dementia-related psychosis taking risperidone, aripiprazole, and olanzapine compared to placebo. No studies have been conducted with oral paliperidone, INVEGA SUSTENNA®, or the 3-month paliperidone palmitate extended-release injectable suspension in elderly patients with dementia. These medicines are not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including paliperidone. Clinical manifestations include muscular rigidity, fever, altered mental status, and altered sensorium. Other signs and symptoms of neurologic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and close medical monitoring, and treatment of any concomitant serious medical problems.

QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. Avoid the use of drugs that also increase QTc interval and in patients with risk factors for prolonged QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

Tardive Dyskinesia (TD): TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose, but can develop after relatively brief treatment at low doses. Elderly female patients appeared to be at increased risk for TD, although it is impossible to predict which patients will develop the syndrome. Prescribing should be consistent with the need to minimize the risk of TD (see full Prescribing Information). Discontinue drug if clinically appropriate. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class are associated with metabolic changes that may increase cardiovascular risk, the likelihood of developing hyperglycemia may be lower with paliperidone palmitate compared to placebo. Paliperidone palmitate extended-release injection was associated with a lower incidence of diabetes compared to risperidone extended-release tablets.

Hyperglycemia and Diabetes Mellitus: Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, have been reported in patients treated with all atypical antipsychotics (APS). Patients starting treatment with APS who have or are at risk for diabetes mellitus should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia during treatment should also undergo fasting blood glucose testing. All patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia. Some patients require continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended. The most common adverse reactions in clinical trials in patients with schizophrenia (±5% and twice placebo) were somnolence, sedation, dizziness, akathisia, and extrapyramidal disorder.

Orthostatic Hypotension and Syncope: INVEGA SUSTENNA® may induce orthostatic hypotension in some patients due to its alpha-adrenergic blocking activity. INVEGA SUSTENNA® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, treatment with antihypertensive medications). Monitoring should be considered in patients for whom this may be of concern.

Falls: Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including INVEGA SUSTENNA® and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Leukopenia, Neutropenia and Agranulocytosis have been reported with antipsychotics, including INVEGA SUSTENNA®. In patients with a history of clinically significant low white blood cell count (WBC)/absolute neutrophil count (ANC) or drug-induced leukopenia/neutropenia, perform a complete blood count frequently during the first few months of therapy. Consider discontinuing INVEGA SUSTENNA® at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue INVEGA SUSTENNA® in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC until recovery.

Hyperprolactinemia: As with other drugs that antagonize dopamine D₂ receptors, INVEGA SUSTENNA® elevates prolactin levels, and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.

Potential for Cognitive and Motor Impairment: Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA SUSTENNA®. INVEGA SUSTENNA® has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities that require mental alertness such as operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA SUSTENNA® does not adversely affect them.

Seizures: INVEGA SUSTENNA® should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold. Conditions that lower seizure threshold may be more prevalent in patients 65 years or older.

Administration: For intramuscular injection only by a healthcare professional using only the needles provided in the INVEGA SUSTENNA® kit. Care should be taken to avoid inadvertent injection into a blood vessel.

Drug Interactions: Strong CYP3A4/P-glycoprotein (P-gp) inducers: Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St. John’s Wort) during a dosing interval for INVEGA SUSTENNA®. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended-release tablets.

Pregnancy/Nursing: INVEGA SUSTENNA® may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare professional if they become pregnant or intend to become pregnant during treatment with INVEGA SUSTENNA®. Patients should be advised that there is a pregnancy registry that monitors outcomes in women exposed to INVEGA SUSTENNA® during pregnancy. INVEGA SUSTENNA® can pass into human breast milk. The benefits of breastfeeding should be considered along with the mother’s clinical need for INVEGA SUSTENNA® and any potential adverse effects on the breastfed infant from INVEGA SUSTENNA® or the mother’s underlying condition.

Commonly Observed Adverse Reactions for INVEGA SUSTENNA®: The most common adverse reactions in clinical trials in patients with schizophrenia (±5% and twice placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder.

Before prescribing INVEGA SUSTENNA®, please review the full Prescribing Information, including Boxed WARNING, available at www.InvegaSustennahcp.com. Please see Brief Summary of full Prescribing Information on following pages of this advertisement.

REFERENCES:
INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

Brief Summary

BEFORE PRESCRIBING INVEGA SUSTENNA®, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA SUSTENNA® is not approved for use in patients with dementia-related psychosis. [see Warnings and Precautions].

INDICATIONS AND USAGE
INVEGA SUSTENNA® (paliperidone palmitate) is indicated for the treatment of:
• Schizophrenia in adults [see Clinical Studies (14.1) in Full Prescribing Information].
• Schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants [see Clinical Studies (14.2) in Full Prescribing Information].

CONTRAINDICATIONS
INVEGA SUSTENNA® is contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the INVEGA SUSTENNA® formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone and in patients treated with paliperidone. Paliperidone palmitate is converted to paliperidone, which is a metabolite of risperidone.

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotics, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious in nature. Observational studies suggest that similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA SUSTENNA® is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions].

Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. No studies have been conducted with oral paliperidone, INVEGA SUSTENNA®, or the 3-month paliperidone palmitate extended-release injectable suspension in elderly patients with dementia. These medicines are not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions].

Neuroleptic Malignant Syndrome
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms. The treatment of established NMS generally requires discontinuation of antipsychotic drugs. In some instances, antipsychotic medication may be cautiously re-administered at a reduced dose, in patients in whom NMS does not respond to this regimen. The presence of severe extrapyramidal symptoms may mask the underlying metabolic disturbance.

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

QT Prolongation
Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of Torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia, (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital QT prolongation or genetic QT prolongation.

The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia. In the QT study (n=141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted decrease from baseline in QTcLD of 12.3 msec (90% CI: 8.9, 15.6) on day 8 at 15 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release (Cmax ss = 113 ng/mL) was more than 2-fold the exposure observed with the maximum recommended 234 mg dose of INVEGA SUSTENNA® administered in the deltoid muscle (predicted median Cmax ss = 50 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which Cmax ss = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6, 10.1) on day 2 at 1.5 hours post-dose.

In the three fixed-dose efficacy studies of oral paliperidone extended release in subjects with schizophrenia, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the oral paliperidone 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec).

In the four fixed-dose efficacy studies of INVEGA SUSTENNA® in subjects with schizophrenia and in the long-term study in subjects with schizoaffective disorder, no subject experienced a change in QTcLD exceeding 80 msec and no subject had a QTcLD value > 500 msec at any time. In the maintenance study in subjects with schizophrenia, no subject had a QTcLD change > 80 msec, and one subject had a QTcLD value of 507 msec (Bazett’s QT corrected interval (QTcB) value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

Tardive Dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of tardive dyskinesia appears to be common among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA SUSTENNA® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA SUSTENNA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA SUSTENNA® despite the presence of the syndrome.

Metabolic Changes
Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have been reported in patients...
INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

INVEGA SUSTENNA® was associated with a mean change in glucose of +0.3 mg/dL (n=131) compared with a mean change of -0.4 mg/dL at Week 29 (n=109) and +6.8 mg/dL at Week 53 (n=100).

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Pooled data from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 1.

Table 1: Change in Fasting Glucose from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>Placebo</th>
<th>39 mg</th>
<th>78 mg</th>
<th>156 mg</th>
<th>234 mg</th>
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<tr>
<td>Serum Glucose</td>
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<tr>
<td>Change from baseline</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Proportion of Patients with Shifts</td>
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<tr>
<td>n=367</td>
<td>n=86</td>
<td>n=244</td>
<td>n=238</td>
<td>n=110</td>
<td>n=126</td>
<td>n=115</td>
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<tr>
<td>-1.3</td>
<td>1.3</td>
<td>3.5</td>
<td>0.1</td>
<td>3.4</td>
<td>1.8</td>
<td>-0.2</td>
</tr>
</tbody>
</table>

^ Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. [see Clinical Studies (14.1) in Full Prescribing Information].

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose available (234 mg) was evaluated, INVEGA SUSTENNA® was associated with a mean change in glucose of -0.4 mg/dL at Week 29 (n=109) and +6.8 mg/dL at Week 53 (n=100). During the initial 25-week open-label period of a long-term study in subjects with schizoaffective disorder, INVEGA SUSTENNA® was associated with a mean change in glucose of +5.2 mg/dL (n=518). At the endpoint of the subsequent 15-month double-blind period of the study, INVEGA SUSTENNA® was associated with a mean change in glucose of +0.3 mg/dL (n=131) compared with a mean change of +4.0 mg/dL in the placebo group (n=120).

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose available (234 mg) was evaluated, INVEGA SUSTENNA® was associated with a mean change in glucose of -0.4 mg/dL at Week 29 (n=109) and +6.8 mg/dL at Week 53 (n=100).

INVEGA SUSTENNA® extended-release injectable suspension, for intramuscular use

Table 2: Change in Fasting Lipids from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

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<td>1.8</td>
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<td>Placebo 39 mg</td>
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<tr>
<td>Change from baseline</td>
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<tr>
<td>n=367</td>
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<th>Change from baseline</th>
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<td>-1.3</td>
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| LDL |
| Change from baseline |
| -1.3 | 1.3 | 3.5 | 0.1 | 3.4 | 1.8 | -0.2 |

| HDL |
| Change from baseline |
| -1.3 | 1.3 | 3.5 | 0.1 | 3.4 | 1.8 | -0.2 |

| Triglycerides |
| Change from baseline |
| -1.3 | 1.3 | 3.5 | 0.1 | 3.4 | 1.8 | -0.2 |

^ Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. [see Clinical Studies (14.1) in Full Prescribing Information].

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose available (234 mg) was evaluated, the mean changes from baseline in lipid values are presented in Table 3.

Table 3: Change in Fasting Lipids from Long-term Open-label Pharmacokinetic and Safety Study in Subjects with Schizophrenia

<table>
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<tr>
<th>INVEGA SUSTENNA®</th>
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<tr>
<td>Week 29</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>39 mg</td>
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<tr>
<td>Change from baseline (mg/dL)</td>
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<tr>
<td>Cholesterol</td>
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<tr>
<td>LDL</td>
</tr>
<tr>
<td>HDL</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
</tbody>
</table>

| HDL |
| Change from baseline (mg/dL) | n=112 | n=107 | n=110 |
| Cholesterol | -1.2 | 0.1 |
| LDL | -2.7 | -2.3 |
| HDL | -0.8 | -2.6 |
| Triglycerides | 16.2 | 37.4 |

^ Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. [see Clinical Studies (14.1) in Full Prescribing Information].

In a long-term open-label pharmacokinetic and safety study in subjects with schizophrenia in which the highest dose available (234 mg) was evaluated, the mean changes from baseline in lipid values are presented in Table 3.

Table 4: Change in Fasting Lipids from an Open-Label and Double-Blind Periods of a Long-Term Study in Subjects with Schizoaffective Disorder

<table>
<thead>
<tr>
<th>INVEGA SUSTENNA®</th>
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<tr>
<td>Placebo INVEGA SUSTENNA®</td>
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<tr>
<td>Double-Blind Period</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>39 mg</td>
</tr>
<tr>
<td>Change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Cholesterol</td>
</tr>
<tr>
<td>LDL</td>
</tr>
<tr>
<td>HDL</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in body weight and the proportion of subjects meeting a weight gain criterion of ≥ 7% of body weight from the four placebo-controlled (one 9-week and three 13-week), fixed-dose studies in subjects with schizophrenia are presented in Table 5.</td>
</tr>
</tbody>
</table>
In the four fixed-dose efficacy studies in subjects with schizophrenia, orthostatic hypotension was reported as an adverse event by <1% (3/1293). Prior to the double-blind phase (during the 25-week open-label phase of the long-term maintenance trial), the mean (SD) serum prolactin values at baseline were 14.9 (22.3) ng/mL in males (N=490) and 35.2 (39.6) ng/mL in females (N=358). At the end of the open-label phase, mean (SD) prolactin values were 24.7 (22.5) ng/mL in males (N=470) and 59.5 (38.1) ng/mL in females (N=353). During the 33-week double-blind phase, 11 females (13.9%) in the INVEGA SUSTENNA® group had 14 potentially prolactin-related adverse reactions (hyperprolactinemia N=3; blood prolactin increased N=4; libido decreased N=1; amenorrhea N=3; galactorrhea N=3), while 2 females (2.2%) in the placebo group experienced potentially prolactin-related adverse reactions (amenorrhea N=1; breast pain N=1). One male (0.9%) in the INVEGA SUSTENNA® group experienced erectile dysfunction and 1 male (0.9%) in placebo group experienced gynecomastia.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prolactin-related adverse reactions observed in patients with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see Nonclinical Toxicology (13.1) in Full Prescribing Information). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

Table 5: Mean Change in Body Weight (kg) and the Proportion of Subjects with <7% Gain in Body Weight from Four Placebo-Controlled, 9- to 13-Week, Fixed-Dose Studies in Subjects with Schizophrenia

<table>
<thead>
<tr>
<th>INVEGA SUSTENNA®</th>
<th>Placebo</th>
<th>39 mg</th>
<th>78 mg</th>
<th>156 mg</th>
<th>234/234 mg*</th>
<th>234/156 mg*</th>
<th>234/234 mg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=451</td>
<td>n=110</td>
<td>n=280</td>
<td>n=267</td>
<td>n=137</td>
<td>n=144</td>
<td>n=145</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-0.3</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.7</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Gain</td>
<td>&gt;7% increase from baseline</td>
<td>3.3%</td>
<td>6.0%</td>
<td>8.9%</td>
<td>9.0%</td>
<td>5.8%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

* Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks deltoid injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. [see Clinical Studies (14.1) in Full Prescribing Information].

In a long-term open-label pharmacokinetic and safety study in which the highest dose available (234 mg) was evaluated, INVEGA SUSTENNA® was associated with a mean change in weight of +2.4 kg at Week 29 (n=134) and +4.3 kg at Week 53 (n=113).

During the initial 25-week open-label period of a long-term study in subjects with schizoaffective disorder, INVEGA SUSTENNA® was associated with a mean change in weight of +0.5 kg at Week 8 (n=111) and +1.0 kg in subjects with an increase in body weight of ≤7% (n=106). A subgroup had a mean change in weight of +0.6 kg and 13.0% of subjects had an increase in body weight of >7% (n=161). All placebo subjects had an increase in body weight of >7% (n=188).

Orthostatic Hypotension and Syncope
Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-adrenergic blocking activity. Syncope was reported in <1% (4/1293) of patients treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/510) of subjects treated with placebo. In the four fixed-dose efficacy studies in subjects with schizophrenia, orthostatic hypotension was reported as an adverse event by <1% (2/1293) of INVEGA SUSTENNA®-treated subjects compared to 0% (0/510) with placebo. Incidences of orthostatic hypotension and syncope in the long-term studies in subjects with schizophrenia and schizoaffective disorder were similar to those observed in the short-term studies.

INVEGA SUSTENNA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Falls
Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including INVEGA SUSTENNA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications), monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis
In clinical trial and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including INVEGA SUSTENNA®. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of INVEGA SUSTENNA® at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue INVEGA SUSTENNA® in patients with severe neutropenia (absolute neutrophil count <1000/mm3) and follow their WBC until recovery.

Hyperprolactinemia
Like other drugs that antagonize dopamine D2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Amenorrhea, galactorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Seizures
In the four fixed-dose double-blind placebo-controlled studies in subjects with schizophrenia, <1% (1/1293) of subjects treated with INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.
Like other antipsychotic drugs, INVEGA SUSTENNA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

**Dysphagia**

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. INVEGA SUSTENNA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

**Priapism**

Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA SUSTENNA®, priapism has been reported with oral paliperidone during postmarketing surveillance. Severe priapism may require surgical intervention.

**Disruption of Body Temperature Regulation**

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA SUSTENNA® to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

**ADVERSE REACTIONS**

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis [see Boxed Warning and Warnings and Precautions]
- Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis [see Warnings and Precautions]
- Neuroleptic malignant syndrome [see Warnings and Precautions]
- QT prolongation [see Warnings and Precautions]
- Tardive dyskinesia [see Warnings and Precautions]
- Metabolic changes [see Warnings and Precautions]
- Orthostatic hypotension and syncope [see Warnings and Precautions]
- Falls [see Warnings and Precautions]
- Leukopenia, neutropenia, and agranulocytosis [see Warnings and Precautions]
- Hyperprolactinemia [see Warnings and Precautions]
- Potential for cognitive and motor impairment [see Warnings and Precautions]
- Seizures [see Warnings and Precautions]
- Dysphagia [see Warnings and Precautions]
- Priapism [see Warnings and Precautions]
- Disruption of body temperature regulation [see Warnings and Precautions]

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

**Patient Exposure**

The data described in this section are derived from a clinical trial database consisting of a total of 2817 subjects (approximately 1705 patient-years exposure) with schizophrenia who received at least one dose of INVEGA SUSTENNA® in the recommended dose range of 39 mg to 234 mg and a total of 510 subjects with schizoaffective disorder. Among the 3817 INVEGA SUSTENNA®-treated subjects, 1293 received INVEGA SUSTENNA® in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 489 received INVEGA SUSTENNA® in the maintenance trial (median exposure 229 days during the initial 33-week open-label phase of this study, of whom 205 continued to receive INVEGA SUSTENNA® during the double-blind placebo-controlled phase of this study [median exposure 171 days]), and 1675 received INVEGA SUSTENNA® in non-placebo controlled trials (three noninferiority active-comparator trials, one long-term open-label pharmacokinetic and safety study, and an injection site [ deltoid-gluteal] cross-over trial). One of the 13-week studies included a 234 mg INVEGA SUSTENNA® initiation dose followed by treatment with either 156 mg, 115 mg, or 234 mg every 4 weeks.

The safety of INVEGA SUSTENNA® was also evaluated in a 15-month, long-term study comparing INVEGA SUSTENNA® to selected oral antipsychotic therapies in adult subjects with schizophrenia. A total of 226 subjects received INVEGA SUSTENNA® during the 15-month, open-label period of this study; 218 subjects received selected oral antipsychotic therapies. The safety of INVEGA SUSTENNA® was similar to that seen in previous double-blind, placebo-controlled clinical trials in adult subjects with schizophrenia. The safety of INVEGA SUSTENNA® was also evaluated in a long-term study in adult subjects with schizoaffective disorder. A total of 667 subjects received INVEGA SUSTENNA® during the initial 25-week open-label period of this study (median exposure 147 days); 164 subjects continued to receive INVEGA SUSTENNA® during the 15-month double-blind placebo-controlled period of this study (median exposure 446 days). Adverse reactions that occurred more frequently in the INVEGA SUSTENNA® than the placebo group (a 2% difference or more between groups) were weight increased, nasopharyngitis, headache, hyperprolactinemia, and pyrexia.

**Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials**

**Commonly Observed Adverse Reactions:** The most common (at least 5% in any INVEGA SUSTENNA® group) and likely drug-related (adverse events for which the drug rate is at least twice the placebo rate) adverse reactions from the double-blind, placebo-controlled trials in subjects with schizophrenia were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder. No occurrences of adverse events reached this threshold in the long-term double-blind, placebo-controlled study in subjects with schizoaffective disorder.

**Discontinuation of Treatment Due to Adverse Events:** The percentage of subjects who discontinued due to adverse events in the four fixed-dose, double-blind, placebo-controlled schizophrenia trials were similar for INVEGA SUSTENNA® and placebo-treated subjects.

The percentage of subjects who discontinued due to adverse events in the open-label period of the long-term study in subjects with schizoaffective disorder did not differ by drug. Due to the double-blind, placebo-controlled period of that study, the percentages of subjects who discontinued due to adverse events were 5.5% and 1.8% in INVEGA SUSTENNA®- and placebo-treated subjects, respectively.

**Dose-Related Adverse Reactions:** Based on the pooled data from the four fixed-dose, double-blind, placebo-controlled trials in subjects with schizophrenia, among the adverse reactions that occurred with ≥ 2% incidence in the subjects treated with INVEGA SUSTENNA®, only akathisia increased with dose. Hyperprolactinemia also exhibited a dose relationship, but did not occur at ≥ 2% incidence in INVEGA SUSTENNA®-treated subjects from the four fixed-dose studies.

**Adverse Reactions Occurring at an Incidence of 2% or More in INVEGA SUSTENNA®-Treated Patients:** Table 6 lists the adverse reactions reported in 2% or more of INVEGA SUSTENNA®-treated subjects at a greater proportion than in the placebo group than in the placebo group with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials.

**Table 6: Incidences of Adverse Reactions 2% or More of INVEGA SUSTENNA®.**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Placebo (N=312)</th>
<th>INVEGA SUSTENNA® (N=130)</th>
<th>INVEGA SUSTENNA® (N=163)</th>
<th>INVEGA SUSTENNA® (N=302)</th>
<th>INVEGA SUSTENNA® (N=312)</th>
<th>INVEGA SUSTENNA® (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total percentage of subjects with adverse reactions</td>
<td>70</td>
<td>75</td>
<td>68</td>
<td>69</td>
<td>63</td>
<td>60</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal discomfort/ abdominal pain upper</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tootache</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>5</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>2</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
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<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Fatigue</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>2</td>
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<td>0</td>
<td>2</td>
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<td>Nasopharyngitis</td>
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<td>0</td>
<td>0</td>
<td>2</td>
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<td>Upper respiratory tract infection</td>
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<td>2</td>
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<tr>
<td>Urinary tract infection</td>
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<td>0</td>
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<td>1</td>
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<td>Investigations</td>
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<td>1</td>
<td>4</td>
<td>4</td>
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<td>1</td>
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<tr>
<td>Weight increased</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Musclekeletal and connective tissue disorders</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Musclekeletal stiffness</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>1</td>
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<td>1</td>
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<tr>
<td>Pain in extremity</td>
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<td>0</td>
<td>2</td>
<td>2</td>
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<td>3</td>
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<tr>
<td>Nervous system disorders</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Dizziness</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>4</td>
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<tr>
<td>Extrapyramidal disorder</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td>15</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Somnolence/ sedation</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>
Adverse reactions for which the INVEGA SUSTENNA® incidence was equal to or less than placebo are not listed in the table, but included the following: dyspepsia, psychotic disorder, schizophrenia, and tremor. The following terms were combined: somnolence/sedation, breast tenderness/breast pain, abdominal discomfort/abdominal pain, and tachycardia/sinus tachycardia/heart rate increased. All injection site reaction-related adverse reactions were collapsed and are grouped under “Injection site reactions”.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of INVEGA SUSTENNA®

The following list does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have significant clinical implications.

Cardiac disorders: atrioventricular block first degree, bradycardia, bundle branch block, palpitations, postural orthostatic tachycardia syndrome, tachycardia

Ear and labyrinth disorders: vertigo

Eye disorders: eye movement disorder, eye rolling, oculogyric crisis, vision blurring

Gastrointestinal disorders: constipation, dyspepsia, flatulence, salivary hypersecretion

Immune system disorders: hypersensitivity

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, electrocardiogram abnormal

Metabolism and nutrition disorders: decreased appetite, hyperinsulinemia, increased appetite

Musculoskeletal and connective tissue disorders: arthralgia, joint stiffness, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, nuchal rigidity

Nervous system disorders: bradykinesia, cerebrovascular accident, cogwheel rigidity, convulsion, dizziness postural, drooling, dysarthria, dyskinesia, dystonia, hypertonia, lethargy, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope

Psychiatric disorders: insomnia, libido decreased, restless legs

Reproductive system and breast disorders: amenorrhea, breast discharge, breast enlargement/breast swelling, breast tenderness/breast pain, ejaculation disorder, erectile dysfunction, galactorrhea, gynecomastia, menstrual disorder, menstruation delayed, menstruation irregular, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: nasal congestion

Skin and subcutaneous tissue disorders: drug eruption, pruritus, pruritus generalized, rash, urticaria

Demographic Differences

An examination of population subgroups in the double-blind placebo-controlled trials did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects 65 years of age and older.

Extrapyramidal Symptoms (EPS)

Pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials in adult subjects with schizophrenia provided information regarding EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score which broadly evaluates parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score which evaluates akathisia, (3) the Abnormal Involuntary Movement Scale scores which evaluates dyskinesia, and (4) use of anticholinergic medications to treat EPS (Table 7) and (5) incidence of spontaneous reports of EPS (Table 8).

Hypertension 1 2 1 1 1 1 0

Agitation 7 10 5 9 8 5 4

Anxiety 7 8 5 3 5 6 6

Nightmare <1 2 0 0 0 0 0

Respiratory, thoracic and mediastinal disorders: cough 2 3 1 0 1 1 1

Vascular disorders

Hypertension 1 2 1 1 1 1 0

Percentages are rounded to whole numbers. Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA SUSTENNA® dose groups and which occurred at a greater incidence than in the placebo group.

Table 6: Incidences of Adverse Reactions 2% or More of INVEGA SUSTENNA®

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Placebo (N=510)</th>
<th>39 mg (N=130)</th>
<th>78 mg (N=302)</th>
<th>156 mg (N=312)</th>
<th>234/29 mg (N=160)</th>
<th>234/156 mg (N=165)</th>
<th>234/234 mg (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>7</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Nightmares &lt;1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough 2</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension 1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

INVEGA SUSTENNA® (paliperidone palmitate)

Extended-release injectable suspension, for intramuscular use

Table 7: Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication – Schizophrenia Studies in Adults

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Placebo (N=262)</th>
<th>39 mg (N=130)</th>
<th>78 mg (N=223)</th>
<th>156 mg (N=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Parkinsonism a</td>
<td>9</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Akathisia b</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Dyskinesia c</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Use of Anticholinergic Medications d</td>
<td>12</td>
<td>10</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 8: Extrapyramidal Symptoms (EPS)-Related Events by MedDRA Preferred Term – Schizophrenia Studies in Adults

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Placebo (N=262)</th>
<th>39 mg (N=130)</th>
<th>78 mg (N=223)</th>
<th>156 mg (N=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Parkinsonism a</td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Hyperkinesia</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dyskinesia</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Dystonia</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Parkinsonism group includes: Extrapyramidal disorder, hypertonia, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia

Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness

Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia

Dystonia group includes: Dystonia, muscle spasms

The results across all phases of the maintenance trial in subjects with schizophrenia exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, the proportions of parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA SUSTENNA® 156 mg group (18% and 11%, respectively) than in the INVEGA SUSTENNA® 78 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

In the 13-week study in subjects with schizophrenia involving 234 mg initiation dosing, the incidence of any EPS was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA SUSTENNA® 234/39 mg, 234/156 mg, and 234/234 mg groups, respectively.

Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the placebo (4.9%) and INVEGA SUSTENNA® 234/156 mg (4.8%) and 234/234 mg (5.5%) groups, but at a lower rate in the 234/39 mg group (1.3%).

In the long-term study in subjects with schizoaffective disorder, EPS reported during the 25-week open-label INVEGA SUSTENNA® treatment included hyperkinesia (12.3%), parkinsonism (8.7%), tremor (5.4%), dyskinesia (2.5%), and dystonia (2.1%). During the 15-month double-blind treatment, the incidence of any EPS was similar to that of the placebo group (8.5% and 7.1% respectively). The most commonly reported treatment-emergent EPS-related adverse events (≥2%) in any treatment group in the double-blind phase of the study (INVEGA SUSTENNA® versus placebo) were hyperkinesia (3.7% vs. 2.9%), parkinsonism (3.0% vs. 1.8%), and tremor (1.2% vs. 2.4%).

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat; swallowing difficulty, difficulty breathing, and/or phonation of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Pain Assessment and Local Injection Site Reactions

In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials in subjects with schizophrenia, the mean intensity of injection pain reported by subjects using a visual analog scale (0 = no pain to 100 = unbearable pain) decreased in all treatment groups from the first to the last injection (placebo: 10.3 to 9.8; 39 mg: 10.2 to 7.7; 78 mg: 10.0 to 9.2; 156 mg: 11.1 to 8.8). The results from both the 9-week, fixed-dose, double-blind, placebo-controlled trial and the double-blind phase of the maintenance trial exhibited comparable findings.
In the 13-week study involving 234 mg initiation dosing in subjects with schizophrenia, occurrences of induration, redness, or swelling, as assessed by blinded study investigators, generally mild in intensity, were observed, and similar in incidence between the INVEGA SUSTENNA® and placebo groups. Investigator ratings of injection pain were similar for the placebo and INVEGA SUSTENNA® groups. Investigator evaluations of the injection site after the first injection for redness, swelling, induration, and pain were rated as absent for 89-100% of subjects in both the INVEGA SUSTENNA® and placebo groups. At Day 92, investigators rated absence of redness, swelling, induration, and pain in 95-100% of subjects in both the INVEGA SUSTENNA® and placebo groups. Additional Adverse Reactions Reported in Clinical Trials with Oral Paliperidone The following is a list of additional adverse reactions that have been reported in clinical trials with oral paliperidone:

**Cardiac disorders:** bundle branch block left, sinu arrhythmia

**Gastrointestinal disorders:** abdominal pain, small intestinal obstruction

**General disorders and administration site conditions:** edema, edema peripheral

**Immune system disorders:** anaphylactic reaction

**Infections and infestations:** rhinitis

**Musculoskeletal and connective tissue disorders:** musculoskeletal pain, torticolis, trismus

**Nervous system disorders:** grand mal convulsion, parkinsonian gait, transient ischemic attack

**Psychiatric disorders:** sleep disorder

**Reproductive system and breast disorders:** breast engorgement

**Respiratory, thoracic and mediastinal disorders:** pharyngolaryngeal pain, pneumonia aspiration

**Skin and subcutaneous tissue disorders:** rash popular

**Vascular disorders:** hypotension, ischemia

**Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of paliperidone; because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: angioedema, ileus, somnambulism, swallowing tongue, thrombotic thrombocytopenic purpura, urinary incontinence, and urinary retention.

Cases of anaphylactic reaction after injection with INVEGA SUSTENNA® have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

In the clinical trials, paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the Adverse Reactions sections of the product insert for those products.

**DRUG INTERACTIONS**

**Drugs Having Clinically Important Interactions with INVEGA SUSTENNA®**

Because paliperidone palmitate is hydrolyzed to paliperidone (see Clinical Pharmacology (12.3) in Full Prescribing Information), results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

**Table 9: Clinically Important Drug Interactions with INVEGA SUSTENNA®**

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine Agonist</strong></td>
<td>paliperidone may antagonize the effect of levodopa and other dopamine agonist</td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>Monitor and manage patient as clinically appropriate</td>
</tr>
<tr>
<td>Intervention</td>
<td>paliperidone may antagonize the effect of levodopa and other dopamine agonist</td>
</tr>
<tr>
<td>Examples</td>
<td>Levodopa, bromocriptine, ropinirole and pramipexole</td>
</tr>
</tbody>
</table>

**Drugs Having No Clinically Important Interactions with INVEGA SUSTENNA®**

Clinically meaningful pharmacokinetic interaction between INVEGA SUSTENNA® and valproate (including valproic acid and divalprox sodium) is not expected. Based on pharmacokinetic studies with oral paliperidone, no dosage adjustment of INVEGA SUSTENNA® is required when administered with valproate (see Clinical Pharmacology (12.3) in Full Prescribing Information). Additionally, no dosage adjustment is necessary for valproate when co-administered with INVEGA SUSTENNA® (see Clinical Pharmacology (12.3) in Full Prescribing Information).

**Pharmacokinetic interaction between lithium and INVEGA SUSTENNA®** is also unlikely.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. In vitro studies indicate that CYP2D6 and CYP3A4 may be involved in paliperidone metabolism; however, there is no evidence in vivo that inhibited or induced CYP enzymes significantly affect the metabolism of paliperidone. Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19; an interaction with inhibitors or inducers of these isozymes is unlikely. (see Clinical Pharmacology (12.3) in Full Prescribing Information)

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including INVEGA SUSTENNA®, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-3388 or online at http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

**Risk Summary**

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery (see Clinical Considerations). Overall, available data from published epidemiologic studies of pregnant women exposed to paliperidone have not established a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data). There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including INVEGA SUSTENNA®, during pregnancy (see Clinical Considerations). Paliperidone has been detected in plasma in adult subjects up to 126 days after a single-dose administration of INVEGA SUSTENNA® (see Clinical Pharmacology (12.3) in Full Prescribing Information), and the clinical significance of INVEGA SUSTENNA® administered before pregnancy or anytime during pregnancy is not known.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

In animal reproduction studies, there were no treatment related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 10 times the maximum recommended human dose (MRHD) of 234 mg paliperidone based on mg/m² body surface area. There were no increases in fetal abnormalities when pregnant rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg of paliperidone based on mg/m² body surface area. Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone (see Animal data).

**Clinical Considerations**

*Disease-associated maternal and/or embryo/fetal risk*

There is a risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

*Fetal/Neonatal Adverse Reactions*

Extrapiramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including INVEGA SUSTENNA®, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates exhibiting extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.
INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use

Data
Human Data
Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study conducted in the U.S. involving 9600 women treated with risperidone or the parent compound of paliperidone, demonstrated placental passage of risperidone and paliperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an increased risk of major birth defects. There was a small decrease in the risk of major birth defects (RR=0.87, 95% CI 0.75-1.01) and of cardiac malformations (RR=1.06, 95% CI 0.48-2.34). A cohort study of 4566 women exposed to the parent compound of paliperidone, risperidone, during the first trimester of pregnancy found no increased risk. However, there is no mechanism of action to explain the difference in malformation rates.

Animal Data
There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate extended-release injectable suspension during the period of organogenesis at doses up to 250 mg/kg, which is 10 times MRHD of 234 mg paliperidone based on mg/m² body surface area. In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated orally with paliperidone during the period of organogenesis with up to 8 times the MRHD of 12 mg based on mg/m² body surface area.

Additional reproduction toxicity studies were conducted with orally administered risperidone, which is extensively converted to paliperidone. Cleat palate was observed in the offspring of pregnant mice treated with risperidone at 3 to 4 times the MRHD of 10 mg/kg. Maternal toxicity occurred at 4 times the MRHD. There was no evidence of teratogenicity in embryo-fetal developmental toxicity studies with risperidone in rats and rabbits at doses up to 6 times the MRHD of 16 mg/day risperidone based on mg/m² body surface area. Increased neuronal cell death occurred in the fetal brains of the offspring of pregnant rats treated at 0.5 to 1.2 times the MRHD; the postnatal development and growth of the offspring was delayed.

In rat reproduction studies with risperidone, pup deaths occurred at oral doses which are less than the MRHD of risperidone based on mg/m² body surface area; it is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams (see RISPERIDAL® package insert).

Lactation
Risk Summary
Limited data from published literature report the presence of paliperidone in human breast milk. There is no information on the effects on the breastfed infant or the effects on milk production; however, there are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to paliperidone’s parent compound, risperidone (see Clinical Considerations). Paliperidone has been detected in the milk of adult subjects up to 126 days after a single-dose administration of INVEGA SUSTENNA® [see Clinical Pharmacology (12.3) in Full Prescribing Information], and the clinical significance on the breastfed infant is not known. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for INVEGA SUSTENNA® and any potential adverse effects on the breastfed child from INVEGA SUSTENNA® or from the mother’s underlying condition.

Clinical Considerations
Infants exposed to INVEGA SUSTENNA® through breast milk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

Females and Males of Reproductive Potential
Infertility
Females
Based on the pharmacologic action of paliperidone (D2 receptor antagonism), treatment with INVEGA SUSTENNA® may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential [see Warnings and Precautions (5.10)].

Females
Safety and effectiveness of INVEGA SUSTENNA® in patients <18 years of age have not been established.

Juvenile Animal Studies
In a study in which juvenile rats were treated with oral paliperidone from days 24 to 32 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.83 mg/kg/day, which produced plasma levels (AUC) of paliperidone similar to those in adolescents dosed at 12 mg/day. No other consistent effects on neurobehavioral or endocrine parameters were seen up to the highest dose tested (2.5 mg/kg/day), which produced plasma levels of paliperidone 2-3 times those in adolescents.

Juvenile dogs were treated for 40 weeks with oral risperidone, which is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

Hepatic Impairment
Paliperidone is extensively metabolized to paliperidone in animals and humans, at doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen with a no-effect dose of 0.31 mg/kg/day, which produced plasma levels (AUC) of risperidone plus paliperidone which were similar to those in children and adolescents receiving the MRHD of risperidone. In addition, a delay in sexual maturation was seen at all doses in both males and females. The above effects showed little or no reversibility in females after a 12-week drug-free recovery period.

Geriatric Use
Clinical studies of INVEGA SUSTENNA® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment [see Clinical Pharmacology (12.3) in Full Prescribing Information], who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, adjust dose based on renal function [see Dosage and Administration (2.5) in Full Prescribing Information].

Renal Impairment
INVEGA SUSTENNA® is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min). Dose reduction is recommended for patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min) [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in Full Prescribing Information].

Hepatic Impairment
INVEGA SUSTENNA® has not been studied in patients with hepatic impairment.

Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment [Clinical Pharmacology (12.3) in Full Prescribing Information].

Patients with Parkinson's Disease or Lewy Body Dementia
Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to INVEGA SUSTENNA®. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

DRUG ABUSE AND DEPENDENCE
Controlled Substance
INVEGA SUSTENNA® (paliperidone) is not a controlled substance.

Abuse
Paliperidone has not been systematically studied in animals or humans for its potential for abuse.

Dependence
Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

OVERDOSAGE
Human Experience
No cases of overdose were reported in premarketing studies with INVEGA SUSTENNA®. Because INVEGA SUSTENNA® is to be administered by healthcare professionals, the potential for overdosage by patients is low.

While experience with paliperidone overdose is limited, among the few cases of overdose reported in premarketing trials with oral paliperidone, the highest estimated ingestion was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone’s known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypertension, and QT prolongation. Torsades de pointes and ventricular Fibrillation have been observed in a patient in the setting of overdose with oral paliperidone.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

Management of Overdosage
Contact a Certified Poison Control Center for the most up to date information on the management of INVEGA SUSTENNA® overdose (1-800-222-1222 or www.poisong.org). Provide supportive care, including close medical supervision and monitoring. Treatment should consist of general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosage. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures. There is no specific antidote to paliperidone.

Consider the prolonged-release characteristics of INVEGA SUSTENNA® and the long apparent half-life of paliperidone when assessing treatment needs and recovery.

INVEGA SUSTENNA® (paliperidone palmitate) Extended-Release Injectable Suspension

Product of Ireland
Manufactured by: Janssen Pharaceutica NV Beerse, Belgium
Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560
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INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use
Discrepancies Between Men and Women Show Up in ADHD Prescriptions

Because ADHD presents differently in female patients than it does in male patients, the disorder has been underdiagnosed in women for years.

By Kenny Walter

Women with attention-deficit/hyperactivity disorder (ADHD) have been underdiagnosed for years, partly because their particular presentation tends to lead them to meeting fewer ADHD diagnostic criteria, and thus they often receive correct diagnoses much later than their male counterparts.

In a recent study published in *PLoS One,* a team led by Francien M. Kok, MSc, of the Department of Clinical and Developmental Neuropsychology, University of Groningen, in the Netherlands, examined differences by sex in prescription rates and the efficacy of pharmacotherapy treatment in female ADHD patients, while identifying potential gaps in the scientific knowledge.

This delay is not seen in adult-onset ADHD, where the mean age at the time of diagnosis has been estimated at 32.7 years with no significant differences between men and women. However, recent studies show female patients are increasingly being identified as having ADHD.

Male patients with ADHD tend to show more of what are defined as “core” symptoms—including inattentiveness, hyperactivity, and impulsivity—than do female patients, who often present instead with mood or emotional dysregulation, making differential diagnosis difficult. This often leads to the misdiagnosis of depression or a mood or anxiety disorder.

The investigators searched electronic databases to identify all published studies on female-specific effects of stimulants and nonstimulants in the treatment of ADHD. Of the 2672 studies identified, 21 (7 on prescription rates and 14 on the effects of pharmacotherapy) met the inclusion criteria for the analysis.

The investigators found that female patients received significantly fewer prescriptions for ADHD than male patients, according to 6 of the 7 ADHD prescription rate studies, while each of the 14 studies on effectiveness found at least 1 sex-related difference in the effects of ADHD pharmacotherapies.

The investigators examined methylphenidate (MPH), dextroamphetamine (dexAMP), mixed amphetamine salts, lisdexamfetamine, atomoxetine (ATX), guanfacine, and clonidine use in adolescents. They found that girls received about one-third of the prescriptions boys in this age group did (25.2% vs 74.8%). Girls were also significantly less likely to be prescribed MPH than boys (55.8% vs 69.7%; d = 0.33).

However, no significant differences by sex were identified in the use of dexAMP, levoamphetamine, pemoline, and methylamphetamine.

“Several sex-differences are demonstrated in the prescription, usage, and efficacy/effectiveness of both stimulant and nonstimulant ADHD pharmacotherapy,” the authors wrote. “A single daily use of MPH may possibly not be optimal for girls with ADHD, and ATX may be a promising medication for girls and women with ADHD. The robustness of this result requires further investigation.”

The worldwide prevalence estimates of ADHD in school-aged children and adolescents vary considerably across countries, from 0.6% to 10.5% in girls and 2.8% to 14.4% in boys. Reported female to male ratios also vary considerably: between 1:3 and 1:1.5 in population-based studies and between 1:5 and 1:9 in clinical samples.

However, ADHD has been diagnosed more frequently across both sexes in the past 15 years.

REFERENCE

ADHD and Autism Are Associated With Increased Hospital Stays in Early Childhood

ADHD is linked with increased procedures, including blood transfusions, hospital admissions, and emergency department visits.

By Kenny Walter

Although children with autism spectrum disorder (ASD) or attention-deficit/hyperactivity disorder (ADHD) have health care utilization (HCU) and annual costs 2 to 3 times those of children without these conditions, not much is known about the HCU patterns of these children early in life.

Matthew M. Engelhard, MD, PhD, of the Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, and colleagues quantified the early HCU of children with these disorders to identify condition-specific health trajectories, with the goal of facilitating earlier detection and intervention.

In the study, the investigators examined data about 29,930 patients born between October 1, 2006, and October 1, 2016, with at least 2 well-child visits within the Duke University Health System before age 1 year. Each child was grouped as either ASD (n = 343), ADHD (n = 1175), ASD plus ADHD (n = 140), or no diagnosis, using retrospective billing codes.

The investigators added an additional comparison group defined by a later upper respiratory infection diagnosis.

In the analysis, using logistic regression models, the researchers compared adjusted odds ratios (AORs) for hospital admissions, procedures, emergency department (ED) visits and outpatient clinic encounters before age 1 year among groups.

The team also compared length of hospital encounters among groups using the Mann-Whitney U test.

Overall, ASD was linked to increased procedures (AOR, 1.5; P < .001), including intubation and ventilation (AOR, 2.4; P < .001), as well as outpatient services, including physical therapy (AOR, 3.5; P < .001) and ophthalmology (AOR, 3.1; P < .001).

ADHD was also associated with increased procedures (AOR, 1.41; P < .001), including blood transfusions (AOR, 4.7; P < .001), hospital admissions (AOR, 1.60; P < .001), and ED visits (AOR, 1.58; P < .001).

The median length of hospital stay was longer in both the ASD group (+6.5 h; P < .001) and ADHD group (+3.8 h; P < .001). This was also found in hospital stays (nonbirth) in the ADHD (+1.1 d; P < .001) and ASD + ADHD (+2.4 d; P = .003) arms.

“ASD and ADHD are associated with increased health system utilization in the first year of life, prior to diagnosis,” the authors wrote. “Moreover, the 2 disorders are associated with distinct patterns of early health interactions that could be monitored through the EHR [electronic health record] to stratify patients’ risk of developing ASD and ADHD.”

The researchers want to focus future research on developing predictive models that could be deployed within a health system to inform provider decision-making, making it possible for earlier diagnosis and treatment.

According to the study findings, ASD affects approximately 1.5% of children in the United States, whereas ADHD affects 11%. However, ADHD symptoms are present in approximately 40% to 60% of patients with ASD, and both disorders lead to significantly higher rates of HCU, with considerable financial burdens placed on individuals and families.

Overall, the rates of hospitalization and outpatient clinic visits among children with ASD are about twice those of a child who does not have the disorder. HCPLIVE.COM

REFERENCE

PCOS Increases Risk of Psychiatric, Neurodevelopment Disorders in Offspring

Children of mothers with PCOS need additional psychological support and longer mental health follow-up.

By Samara Rosenfeld

Children born to women with polycystic ovary syndrome (PCOS) are at a greater risk of psychiatric and neurodevelopmental disorders.

The risk further increases if PCOS is combined with the mother being obese, having gestational diabetes, or having a cesarean delivery or if the mother or baby had a medical problem around birth, according to the results of a study by an international group of investigators.

“Our study shows that children of mothers with PCOS are in need of psychological support and longer follow-up for mental health. Health care providers should consider that children born to mothers with PCOS are at high risk of mental health problems, even those born to normal-weight mothers. Counseling for women with PCOS and monitoring of their offspring should be offered routinely in order to help prevent these problems,” first author Xinxia Chen, MD, associate professor at Shandong University, said in a statement.

Chen and a team of investigators from China, Finland, and Sweden included all live births during 1996-2014 in Finland registered in the Drugs and Pregnancy Database and originally identified from the Medical Birth Register. The Finnish Care Register for Health Care (HILMO) was used to identify clinical diagnoses for offspring and mothers. Maternal PCOS was identified from HILMO based on a PCOS diagnosis or anovulatory infertility. Further, the team leveraged HILMO to identify cases of neurodevelopmental or psychiatric disorders, defined as a primary or secondary diagnosis of mood disorders, anxiety disorders, eating disorders, sleeping disorders, personality disorders, intellectual disabilities, specific developmental disorders, attention-deficit/hyperactivity disorder (ADHD), conduct disorders, tic disorders, and other behavioral and emotional disorders.

The team used the Drugs and Pregnancy Database to collect information on maternal age at delivery, parity, country of birth, mother’s marital status at birth, smoking during pregnancy, diagnoses of systemic inflammatory disorders, and psychiatric disorders.

Of more than 1 million offspring, 9.8% received a diagnosis of a neurodevelopmental or psychiatric disorder. A total of 0.6% of children were identified with maternal PCOS and 1.7% with maternal anovulatory infertility. There were increased risks for most neuropsychiatric disorders studied for the offspring with maternal PCOS and those with maternal anovulatory infertility.

The mothers with PCOS versus those without were more likely to be aged at least 30 years, overweight or
obese, first-time pregnant, married, nonsmokers, and undergoing fertility treatment, as well as to have developed gestational diabetes mellitus, preeclampsia, or perinatal problems and to have had a cesarean delivery.

Compared with PCOS-unexposed children, those with mothers with PCOS were at higher risk of any neuropsychiatric disorder (HR, 1.32; 95% CI, 1.27-1.38). For most pediatric neurodevelopmental and psychiatric disorders, there was an increased risk of 30% to 50% in the presence of maternal PCOS. Risk estimates were similar for male (HR, 1.3; 95% CI, 1.24-1.37) and female offspring (HR, 1.36; 95% CI, 1.28-1.45).

In offspring exposed to PCOS, maternal prepregnancy body mass index (BMI) was categorized as overweight in 15.8%, moderately obese in 9.0%, and severely obese in 5.3% of cases. Mothers without PCOS were overweight, moderately obese, and severely obese in 12.1%, 4.4%, and 2.1% of instances, respectively.

The team found that mothers with PCOS who were of normal weight, compared with normal-weight mothers without PCOS, had increased risks of having a child with any neuropsychiatric disorder (HR, 1.2; 95% CI, 1.09-1.32), intellectual disabilities (HR, 1.44; 95% CI, 1.12-1.85), autism spectrum disorder (ASD; HR, 1.39; 95% CI, 1.12-1.73), other behavioral and emotional disorders (HR, 1.38; 95% CI, 1.21-1.57), anxiety disorders (HR, 1.25; 95% CI, 1.08-1.45), and specific developmental disorders (HR, 1.19; 95% CI, 1.08-1.32). Such findings indicate an association between maternal PCOS and adverse neuropsychiatric outcomes in offspring independent of BMI.

There was a significantly higher risk of any neuropsychiatric disorder in offspring born to mothers with PCOS and obesity compared with those with maternal obesity alone. Further, among births to moderately obese mothers without PCOS, there were significantly higher risks of children developing ADHD and conduct disorders (HR, 2.16; 95% CI, 1.74-2.68 vs HR, 1.6; 95% CI, 1.52-1.69), specific developmental disorders (HR, 2.13; 95% CI, 1.84-2.47 vs HR, 1.61; 95% CI, 1.55-1.67), and other behavioral and emotional disorders (HR, 1.89; 95% CI, 1.51-2.36 vs HR, 1.28; 95% CI, 1.2-1.36).

Overall, mood disorders, anxiety disorders, eating disorders, sleeping disorders, intellectual disabilities, specific developmental disorders, ASD, ADHD and conduct disorders, and other behavioral and emotional disorders in offspring were associated with maternal PCOS and/or anovulatory infertility. Additional studies are needed to confirm the results and investigate underlying pathways and mechanisms linking PCOS exposure to long-term neurodevelopmental consequences.

REFERENCE

Our study shows that children of mothers with PCOS are in need of psychological support and longer follow-up for mental health.

—Xinxia Chen, MD

More on HCPLIVE.COM

Samuele Cortese, MD, PhD: The Current State of ADHD Treatment

Samuele Cortese, MD, PhD, professor of child and adolescent psychiatry, University of Southampton, examines the current state of pharmacologic treatment for ADHD.

View video: hcplive.com/view/cortese-current-state-adhd-treatment
Investigators Find Link Between ADHD and Sleep Issues in Adolescents

ADHD symptoms are highly comorbid with insomnia, restless leg syndrome, and snoring.

By Kenny Walter

Both sleep problems and attention-deficit/hyperactivity disorder (ADHD) are relatively common in adolescents, but little is known about the prospective link between sleep and subsequent ADHD symptoms in this patient group.

A team led by Xiachen Liu, of Shandong University’s School of Public Health in China, examined the prospective associations between sleep problems and subsequent ADHD symptoms in a large sample of adolescent patients. Their results were published in the journal *Sleep.*

The Shandong Adolescent Behavior and Health Cohort trial included 7072 adolescents in Shandong. Each patient was initially assessed between November and December 2015 and reassessed 1 year later.

The investigators collected sleep problem, sleep duration, and psychosocial information using a structural questionnaire; they measured ADHD symptoms using the Achenbach Child Behavior Checklist – Youth Self-Report.

At baseline, 7.6% of participants had clinically relevant ADHD symptoms. These symptoms were highly comorbid with sleep problems, including insomnia symptoms, poor sleep quality, symptoms of restless legs syndrome, frequent snoring, and short sleep duration.

Of the 6531 participants without clinically relevant ADHD symptoms at baseline, 4.5% reported clinically relevant ADHD symptoms at the 1-year follow-up.

The investigators also adjusted adolescent and family covariates for insomnia (OR, 2.09; 95% CI, 1.45-3.02), restless legs syndrome (OR, 1.47; 95% CI, 1.02-2.11), and frequent snoring (OR, 2.30; 95% CI, 1.36–3.90), and all 3 were significantly linked to subsequent ADHD symptoms.

"ADHD symptoms and sleep problems are highly comorbid. Insomnia, restless legs syndrome, and frequent snoring appear to be significant predictors of subsequent ADHD symptoms," the authors wrote.

“Our study highlights the importance of assessing and managing sleep problems for prevention and clinical treatment of ADHD symptoms in adolescence.”

In a separate study, researchers examined the relationship between adolescent sleep duration and the likelihood of developing a psychiatric disorder later on in life.

A team led by Bror M. Ranum, of the Department of Psychology, Norwegian University of Science and Technology in Trondheim, Norway, examined the long-term and bidirectional link between the duration of sleep and symptoms of psychiatric disorders for children aged 6, 8, 10, and 12 years.

The population-based cohort study included 799 children who participated in the Trondheim Early Secure Study, in which all time-invariant confounders and baseline levels of study variables were accounted for.

The investigators conducted a representative, stratified random sample of children in the study who were born between January 1, 2003, and December 31, 2004.

In the study, short sleep duration was prospectively tied to symptoms of psychiatric disorders that occurred at younger ages but not older ages. There was no evidence found for the opposite direction of association.

Shorter sleep duration at age 6 years (β [unstandardized regression coefficient] = −.44; 95% CI, −0.80 to −0.08; *P* = .02) and 8 years (β = −0.47; 95% CI, −0.83 to −0.11; *P* = .01) accurately forecast symptoms of emotional disorders 2 years later.

However, shorter sleep duration at age 8 years (β = −0.65; 95% CI, −1.22 to −0.08; *P* = .03) and 10 years (β = −0.58; 95% CI, −1.07 to −0.08; *P* = .02) was associated with symptoms of behavioral disorders 2 years later among boys but not among girls at age 8 years (β = −0.14; 95% CI, −0.52 to 0.24; *P* = .48) or 10 years (β = −0.05; 95% CI, = −0.49 to 0.40; *P* = .84).

REFERENCES

What is the difference between attention-deficit/hyperactivity disorder and attention-deficit disorder?

David W. Goodman, MD: ADHD is the formal diagnosis. Without hyperactivity and impulsivity in adults, the general public will call that ADD, but ADHD is the formal diagnosis. It breaks out into 3 flavors, as I like to call them. You have the inattentive, you have the hyperactive and impulsive, and then you have the combined type. What’s interesting is that from *DSM-IV* to *DSM-5*, we’ve gone from subtypes to presentations. That’s because the children who might have had hyperactivity and impulsivity and would have been a combined type as a child may now be an adult with less hyperactivity and impulsivity. They don’t reach the symptom threshold for a combined type, and they get diagnosed as inattentive. We now go on presentation of symptoms when you see the patient for a comprehensive psychiatric evaluation.

View video: [hcplive.com/clinical-adhd-subtypes](http://hcplive.com/clinical-adhd-subtypes)

What brings patients through your door?

Andrew J. Cutler, MD: Of course, it’s very important to evaluate for the symptoms. That’s what we use in our diagnostic checklist, and that’s what we use to establish a diagnosis. But what often brings people in is not the symptoms per se but the consequences of the symptoms—the negative impact on behavior and on achievement and performance. For instance, children are often brought in because they’re disruptive in school or in class. They can’t sit still. They can’t participate in quiet time or nap time. They may be talking too much. As they get older, there are more cognitive demands. They get in trouble for not paying attention in class, for not doing homework assignments, and for not being able to work independently. Then, as we get into managing adolescents and adults, there can be significant problems with their organizational skills—again, meeting deadlines and tasks and doing things they’re supposed to do.

View video: [hcplive.com/adhd-evaluation](http://hcplive.com/adhd-evaluation)
What is the prevalence and clinical burden of this disorder?
Ann C. Childress, MD: It’s a little different in children versus adults, and it really depends on what source and what country you are looking at. A recent meta-analysis calculated the worldwide prevalence of ADHD [attention-deficit hyperactivity disorder] in children to be about 7.2%, but it’s a bit higher in the United States. As part of the 2016 National Survey of Children’s Health, parents reported whether their children—aged 2 to 17—had ever received a diagnosis, and it totaled about 9.4%, or 6.1 million children who had received the diagnosis at some time in their lives.
Currently, 5.4 million children have the diagnosis. That’s almost 90% of the children ever diagnosed. Two-thirds are currently taking medication, and almost half had received behavioral treatment for ADHD in the past 12 months. In contrast, 23% had never received medication or behavioral treatment. If you look at adults, the World Health Organization estimated the worldwide prevalence of ADHD in adults aged 18 to 44 to be about 2.8%. In the United States, it’s a bit higher—about 4.4%.
View video: hcplive.com/factors-predispose-adhd

What are the challenges associated with diagnosing attention-deficit/hyperactivity disorder?
Theresa Cerulli, MD: What I’d like to point out here is that for adults with ADHD, we don’t have any specific diagnostic and treatment guidelines from the American Psychiatric Association, which can make this a bit more challenging. For children and adolescents, we do have some diagnostic guidelines, right? In 2000 or 2001, the American Academy of Pediatrics came out with the first diagnostic and treatment guidelines for ADHD in children and adolescents.
Those guidelines were updated in 2011. Then they were updated again in October 2019. The American Academy of Pediatrics is now taking into consideration how common comorbidities are with ADHD. There is a key action statement added to those guidelines about looking at not only the core symptoms of ADHD but also the common coexisting conditions—the comorbidities.
I like to say that ADHD often does not travel alone. It has companions with it. ADHD is often seen with things like anxiety and depression.
View video: hcplive.com/diagnosing-adhd

Factors That Predispose for ADHD

What options other than medication do our patients have?
Timothy E. Wilens, MD: Structured therapy such as cognitive behavioral therapies are among the most effective treatments for ADHD symptoms. They’ve been studied as both individual therapies but also as group therapies. It’s been shown that they really do help.
View video: hcplive.com/adhd-evaluation

Nonpharmacologic Strategies for ADHD

Accurately Diagnosing ADHD
Maternal Hypertension Raises Risk of Mental Health Disorders in Children

New research findings suggest that the presence of a maternal hypertensive disorder during pregnancy predicts increased chance of childhood mental disorder, regardless of the mental disorder status of the parents.

By Patrick Campbell

A lthough a renewed emphasis on women’s cardiovascular health recently prompted multiple studies examining long-term impact of cardiovascular disorders, results of a new study suggest that the children of women who have hypertensive disorders during pregnancy may be at a greater risk of mental health disorders.

Using data on a cohort of more than 4500 Finnish women, investigators found that preeclampsia predicts increased risk of childhood mental disorder, regardless of the mental disorder status of either parent. It is the first study to establish such a link.

“The findings emphasize the need for preventive interventions and treatments for maternal hypertensive disorders, since such interventions have the potential...
to benefit both the well-being of the expectant mother and her offspring,” said lead investigator Marius Lahti-Pulkkinen, PhD, of the Department of Psychology and Logopedics at the University of Helsinki in Finland, in a statement. “The findings also shed important new light on the etiology of childhood mental disorders.”

In an attempt to build upon research relating to maternal hypertensive disorders and mental health of children, Lahti-Pulkkinen and colleagues conducted the current study\(^2\) using data from the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study. The investigators identified a cohort of 4743 women from PREDO for their analysis.

PREDO included 4777 Finnish women and their singleton children born between 2006 and 2010, but 34 were excluded from the current study. The age range of the children at the time of analysis was 6.4 to 10.8 years.

Data obtained from the PREDO study included measurements of maternal systolic blood pressure and diastolic blood pressure as well as information related to maternal and paternal mental health disorders. For their analysis, the investigators examined the incidence of any childhood mental disorders, psychological development disorders, and behavioral and emotional disorders as outcomes; all were identified through the use of International Classification of Diseases, Tenth Revision codes.

Covariates included in the investigators’ analysis included maternal smoking status, alcohol use, parity, age at delivery, education level, and lifetime diagnosis of maternal and paternal mental disorders. Other covariates included were presence of paternal hypertensive disorders, offspring sex, and offspring birth year.

Of the 4743 women, 200 had chronic hypertension, 4 had unspecified hypertension, 263 had gestational hypertension, 209 had preeclampsia during the current pregnancy, and 333 had hypertensive disorders only before the current pregnancy.

Results of the investigators’ analyses revealed multiple associations between the severity of risk of childhood mental disorder in offspring on one hand and maternal gestational hypertension, chronic hypertension, and preeclampsia on the other. Investigators noted that the associations seen between mental disorders and preeclampsia (HR, 1.66; 95% CI, 1.14-2.42) and severe preeclampsia (HR, 2.01; 95% CI, 1.08-3.73) were independent of all covariates included.

Additionally, results indicated that the combination of obesity and diabetes with maternal hypertensive disorder increased the cumulative incidence of mental disorders among children from 6.6% to 22.2%.

“While previous studies have shown significant effects of preeclampsia on [attention-deficit/hyperactivity disorder], autism spectrum disorder, and schizophrenia in the offspring, a novel aspect of our findings was that the predisposing effects of maternal preeclampsia extended to any childhood mental disorder in the offspring,” said Lahti-Pulkkinen in the aforementioned statement.

REFERENCES


Findings Connect Prenatal Acetaminophen Exposure With Higher Risk of ADHD

Increased levels of acetaminophen detected in meconium were linked to greater odds of developing ADHD by age 6 to 7 years.

By Jonathan Alicea

Recent study results have found an association between prenatal acetaminophen exposure and an increased risk for attention-deficit/hyperactivity disorder (ADHD), leading the investigators to suggest that the drug’s use during pregnancy should be reevaluated.¹

Despite acetaminophen’s widespread use, the researchers noted increasing concerns that it may impair fetal brain development. This may happen both directly, by inducing oxidative stress and apoptosis in the brain, and indirectly, through disrupting essential developmental hormones.

In this prospective birth cohort study, Brennan Baker, MA, and colleagues at Columbia University Medical Center and Mailman School of Public Health assessed meconium samples for acetaminophen in newborns, then evaluated the same population for ADHD when they were aged 6 or 7 years. The investigators assessed resting-state brain connectivity using MRI, and they assessed attention problems and hyperactivity using the Behavioral Assessment System for Children Parent Report Score. Linear and logistic regressions were used to estimate the associations between meconium
acetaminophen levels and outcomes. Finally, the investigators used causal mediation analysis to test if resting-state brain connectivity mediates the association between prenatal exposure and hyperactivity.

Enrollment occurred between September 2007 and September 2009, and data were collected from September 2007 to January 2020.

By using a direct measurement of prenatal acetaminophen exposure that is unbiased by maternal recall, these results add evidence.

—Brennan Baker, MA, and colleagues

Overall, 345 children (boys, 51.3%) were included in the analysis, and mean age at follow-up was 6.58 years.

Acetaminophen was detected in 199 meconium samples (57.7%), and ADHD was detected in 33 children (9.6%). Acetaminophen detection in meconium was associated with about 2.5-fold increased odds of ADHD compared with nondetection (odds ratio [OR], 2.43; 95% CI, 1.41-4.21).

The investigators further stratified acetaminophen meconium into 3 levels of prevalence. High levels of the drug were associated with a 4-fold increased odds of ADHD (OR, 4.10; 95% CI, 2.41-6.9), whereas lower odds were linked with lower levels of detected acetaminophen (OR, 1.44; 95% CI, 0.79-2.63).

Further, a linear modeling of meconium acetaminophen revealed that each doubling of exposure increased the odds of ADHD by 10% (OR, 1.10; 95% CI, 1.02-1.19).

The team also reported that children born with greater levels of acetaminophen detected in meconium later showed increased negative connectivity between the frontoparietal and default mode network nodes and 6 clusters in the sensorimotor cortices. The investigators noted that this mediated an indirect effect on increased child hyperactivity (14% increase; 95% CI, 1%-26%).

Previous studies have linked use of the pain management medication during pregnancy with increased risk for ADHD, but only 1 other study has directly measured acetaminophen levels.

This team also addressed previous limitations of using and relying on maternal recall of drug use assessed through questionnaires and other similar methods.

“By using a direct measurement of prenatal acetaminophen exposure that is unbiased by maternal recall, these results add evidence in support of the association between prenatal acetaminophen use and child ADHD,” the investigators wrote. “Thus, the association between prenatal acetaminophen and ADHD may be even stronger than previously estimated.”

REFERENCE

David W. Goodman, MD: New Treatments Coming for ADHD

David Goodman, MD, assistant professor of psychiatry and behavioral sciences at Johns Hopkins School of Medicine, explains that at least 29 different ADHD treatments exist, representing numerous medication families, which can lead to some confusion among doctors over what the right therapy for a patient might be. However, options can be important in psychiatry, because many patients do not respond to the first treatment prescribed to them.

View video: hcplive.com/view/goodman-treatments-adhd

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New research suggests that endocrine-disrupting chemical exposure could substantially increase the risk of developing attention-deficit/hyperactivity disorder (ADHD).

A US research team, led by Jessica R. Shoaff, PhD, Channing Division of Network Medicine, Harvard Medical School, Brigham and Women’s Hospital, evaluated the link between exposure to select endocrine-disrupting chemicals during adolescence and ADHD-related behaviors.¹

Currently, ADHD is the most common childhood neurobehavioral disorder, affecting approximately 9.4% of children in the United States. It is believed that prenatal and early childhood exposure to endocrine-disrupting chemicals could be linked to ADHD, but it has not been examined during adolescence.

Endocrine-disrupting chemicals are widely used in consumer products such as food processing and packaging equipment, personal care products, and pharmaceuticals.

In the cross-sectional analysis, the investigators collected data from 205 adolescents in the New Bedford Cohort, an ongoing prospective birth cohort, between June 2011 and June 2014.

The mean age at assessment was 15.3 (SD, 0.7) years old.
Each participant provided spot urine samples and underwent neurodevelopmental testing. The investigators used a repeated-measures analysis with multivariate modified Poisson models to estimate the adjusted relative risk of ADHD-related behaviors associated with exposure to endocrine-disrupting chemicals.

The research team also quantified urinary biomarkers of endocrine-disrupting chemicals or their metabolites, including phthalates, parabens, phenols, and triclocarban. They created summary exposure measures combining biomarker concentrations of chemicals with a shared mechanism of action, exposure pathway, or chemical class.

The investigators assessed behaviors related to ADHD with up to 14 indices from self-, parent-, and teacher-completed behavioral checklists using validated and standardized instruments, particularly using the Conners Attention Deficit Scale and the Behavior Assessment System for Children, Second Edition.

The researchers dichotomized scores on each index to identify those with evidence of a significant behavioral problem, defined by each scale’s interpretive guidelines.

The median urine concentrations were 0.45 μmol/L of σ-antiandrogenic phthalates, 0.13 μmol/L of ΣDEHP metabolites, 0.49 μmol/L of Σpersonal care product phthalates, 0.35 μmol/L of Σparabens, 0.02 μmol/L of Σbisphenols, and 0.02 μmol/L of Σdichlorophenols.

The researchers found 82 scores (40%) consistent with a significant behavioral issue, 39 (19%) of which had a definitive ADHD diagnosis. For each 2-fold increase in the sum of antiandrogenic phthalate concentration, there was a 1.34 (95% CI, 1.00-1.79) increase in the risk of a significant ADHD-related behavior problem.

A 2-fold increase in the sum of dichlorophenols was linked with a 1.15 (95% CI, 1.01-1.32) increased risk of such a problem.

In both cases, the associations were stronger in male participants, but comparisons of sex-specific differences were imprecise.

The results support a further examination of endocrine-disrupting chemicals as a potential risk factor for significant ADHD-related behavior problems.

“Endocrine-disrupting chemicals are used in a wide variety of consumer products resulting in ubiquitous exposure,” the authors wrote. “The study findings suggest that exposure to some of these chemicals, particularly certain phthalates, during adolescence may be associated with behaviors characteristic of ADHD.”

—Jessica R. Shoaff, PhD, and colleagues

The study findings suggest that exposure to some of these chemicals, particularly certain phthalates, during adolescence may be associated with behaviors characteristic of ADHD.”

REFERENCE
Theresa Cerulli, MD: ADHD Students Struggling During COVID-19

The coronavirus disease 2019 pandemic has upended any notion of a traditional school year, making it more difficult for every student to learn. However, the circumstances might be especially daunting for patients with attention-deficit/hyperactivity disorder (ADHD).

In this episode of DocTalk, Theresa Cerulli, MD, a psychiatrist in North Andover, Massachusetts, and a lecturer at Beth Israel Deaconess Medical Center, discusses just how difficult this school year might be for students experiencing ADHD.

LISTEN: hcplive.com/view/cerulli-adhd-students-covid-19

Lungcast: Up Close and Personal With Dr Anthony Fauci

A recent Lungcast episode from HCPLive® and the American Lung Association features Anthony Fauci, MD, the longtime head of the National Institute of Allergy and Infectious Diseases, a world-renowned immunologist, and an ambassador to science-informed public health practice.

Listen as Fauci shares vital insights and perspectives into coronavirus disease 2019 vaccines, SARS-CoV-2 transmission, antibody development, future pandemic preparedness, and the theology that has come to burden the country’s response to the pandemic.

LISTEN: hcplive.com/view/up-close-personal-dr-anthony-fauci

Andrew J. Cutler, MD: Diagnosing ADHD in Pediatric Patients

In an interview with HCPLive®, Andrew J. Cutler, MD, clinical professor of psychiatry at SUNY Upstate Medical University, said he commonly diagnoses attention-deficit/hyperactivity disorder in patients starting from age 6, but it is possible to diagnose it in patients who are as young as 2 or 3 years of age.

VIEW VIDEO: hcplive.com/view/cutler-diagnosing-adhd-pediatric

Eran Orr: The Need For Better ADHD Screening

Although treatment for attention-deficit/hyperactivity disorder (ADHD) has improved over time, diagnostics generally have not.

In an interview with HCPLive®, Eran Orr, founder and CEO of XRHealth, said he is hopeful that new technology could be used to better screen patients for ADHD.