The Adolescent Brain Is Different
Criminal Responsibility and Adolescents

by Peter Ash, MD

Sixteen-year-old John and 2 friends go to a club where they get into a verbal argument with 3 members of a rival gang. After receiving a particularly gross insult, John pulls out a handgun and fires 3 shots at one of the gang members. He misses, but one of his shots hits a 15-year-old girl in the head and kills her. John is tried in adult criminal court and is convicted of murder.

Judges and attorneys who deal with such cases have many questions that involve mental health issues. How morally responsible is the adolescent defendant? How likely is he to offend again? How amenable is he to rehabilitation? How will handling this case in a particular way affect other juveniles? Punishment is often seen as having 4 potential purposes: retribution, incapacitation, rehabilitation, and deterrence. Mental health experts potentially have something to say that is relevant to each of these purposes—both at the level of the individual defendant and at the level of developing social policy for handling offending adolescents (Table 1).

Legal background
This past June, the US Supreme Court decided the case Miller v Alabama, in which the Court held 5 to 4 that youths younger than 18 years could not be given mandatory life without parole.1 This decision does leave open the possibility of a life sentence without parole for a youth, but only after a judge or jury determines that such a sentence is suitable in that particular case.

The Miller v Alabama decision is the latest in a line of cases going back 25 years in which the Supreme Court has increasingly limited the situations in which minors may receive the most extreme punishments, based largely on a theory of reduced culpability. In Thompson v Oklahoma, the Supreme Court held that it was unconstitutional to impose the death penalty on defendants who were younger than 16 years when they committed their offenses.2 The basic logic was laid out by Justice Stevens, who wrote for the majority in 1988: . . . the Court has already endorsed the proposition that less culpability should attach to a crime committed by a juvenile than to a comparable crime committed by an adult. The basis for this conclusion is too obvious to require extended explanation. Inexperience, less education, and less intelligence make the teenager less able to evaluate the consequences of his or her conduct while at the same time he or she is much more apt to be motivated by mere emotion or peer pressure than is an adult. The reasons why juveniles are not trusted with the privileges and responsibilities of an adult also explain why their irresponsible conduct is not as morally reprehensible as that of an adult.2(p569)

In the years since that decision, a good deal of research has put meat on the bones of Justice Stevens’ characterization of adolescent behavior and on the neurobiology that underlies it. In the 2005 case Roper v Simmons, the Supreme Court found that the execution of minors was cruel and unusual punishment and thus unconstitutional, basing a reduced culpability analysis on 3 aspects of adolescence: immaturity with impulsivity, vulnerability to adverse environmental factors, and the fact that an adolescent’s character is not well formed.3(p569) In 2010, using much of the reasoning of Roper v Simmons, the Court found it unconstitutional to sentence adolescents to life without parole for crimes less than murder.4 In cases involving less serious charges, psychiatric assessments may be used in arguing that a case should be tried in juvenile court—an outcome that usually results in less severe penalties.

Criminal responsibility of adolescents
Because children are typically considered insufficiently responsible, their cases are not heard in adult court, while adults are legally presumed fully responsible. Adolescents lie somewhere in the middle of this continuum. A successful insanity defense negate criminal responsibility. Adolescents rarely use an insanity defense, in part because the incidence of psychosis is considerably lower in adolescents than in adults, and in part because youths who are so obviously mentally ill as to qualify for an insanity defense are often not waived to adult court. While it is fairly clear that adolescents overall are less blameworthy than adults, it is often unclear in a particular case how much less blameworthy a particular adolescent is. Psychiatrists may be called on to consult in such cases to assist in determining the adolescent’s culpability.

Developmental considerations of adolescent aggression and impulsivity
One metaphor sometimes used in discussing adolescent aggression is that compared with adults, adolescents have their foot on the gas and have inadequate brakes. The literature reveals a number of key findings about adolescent development that are important to keep in mind when evaluating juvenile offenders for the courts.

For most youths, the onset of serious violence is an adolescent phenomenon, with a peak age of onset at around 16.5 If a person has not acted violently before age 21, the likelihood he or she will ever do so is quite low.

Serious violent offending (defined as aggravated assault, robbery, gang fights, or rape) is surprisingly common in adolescence: the Surgeon General’s report on youth violence noted that 30% to 40% of boys and 16% to 32% of girls had committed a serious violent offense by age 17.6 For most youths, offending is limited to adolescence. About 80% of adolescent violent offenders stop offending when they reach adulthood.

Table 1

<table>
<thead>
<tr>
<th>Mental health issues in punishing adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose of punishment</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Retribution</td>
</tr>
<tr>
<td>Incapacitation</td>
</tr>
<tr>
<td>Rehabilitation</td>
</tr>
<tr>
<td>Deterrence</td>
</tr>
</tbody>
</table>

Table 2

Factors to consider in assessing adolescent culpability

- Appreciation of wrongfulness
- Ability to conform to law
- Developmental course of aggression and impulsivity
- Immaturity: IQ, psychosocial maturity, including time sense, susceptibility to peer pressure, risk taking, ability to empathize
- Environmental circumstances
- Peer group norms
- Out-of-character action
- Incomplete personality development
- Mental illness
- Reactive attitudes toward the offense

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and fewer than half of those who do continue have an adult career of violence that lasts longer than 2 years.6

There is little evidence to suggest that one can accurately predict who will go on to offend as an adult and who will not. Some data suggest that delinquents who continue their criminal behavior into adulthood have different developmental patterns: those who persist in criminal activity tend to have a worsening of impulsiveness and ability to suppress their aggression, rather than the improvement that typically comes with maturation.7

Serious violence is typically the end of a developmental progression of offenses that begins with low-level offenses (vandalism and shoplifting), progresses to nonconfrontational offenses (theft), and then to violent offenses (aggravated assault and rape).8 Delinquents do not begin their antisocial activities by shooting someone.

Finally, adolescent crime is different from adult crime. Adolescents typically offend in groups, while adults typically offend alone. Also, adolescent crime tends to be more impulsive than adult crime.4 Adolescent culpability is a complex concept. A number of factors should be assessed in evaluating the criminal responsibility of an adolescent offender (Table 2).9

Adolescent immaturity
The area that has received the most attention is adolescent immaturity.

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Efficacy
• FANAPT significantly improved overall symptoms in 2 clinical trials, as measured by the Positive and Negative Syndrome Scale (PANSS) (4-week trial) and the Brief Psychiatric Rating Scale (BPRS) (6-week trial).1

Tolerability
• Discontinuation rates due to adverse events were similar for FANAPT (5%) and placebo (5%).1* The most common adverse reactions were dizziness, dry mouth, fatigue, nasal congestion, somnolence, tachycardia, orthostatic hypotension, and weight increase.1

EPS†/Akathisia
• Incidence of EPS and akathisia was similar to placebo.1*
and impulsivity. Cauffman and Steinberg\textsuperscript{10} found that lower levels of psychosocial maturity correlated with more decisions to commit antisocial acts. Moreover, psychosocial maturity was a more significant predictor than age. Considerable research has further refined our views of components of adolescent judgment; such factors as risk-taking, reward-seeking, impulsivity, and self-regulation have been used to argue for mitigation of adolescent culpability.\textsuperscript{11,12}

Over the past decade, there has also been considerable research on adolescent brain development. The findings are consistent with a biological explanation for the behavioral findings in adolescence and point to an evolving understanding of why adolescents overvalue immediate rewards and lack the impulse control of mature adults.\textsuperscript{10,13-15} These findings show that the limbic system, responsible for emotions, matures before the prefrontal cortex, which is responsible for executive functioning. Furthermore, the tracts between the prefrontal cortex and the limbic system continue to be myelinated through adolescence.

These findings are consistent with the hypothesis that the decrease in impulsivity seen with aging into early adulthood is due to delayed maturation of the prefrontal cortex (the brakes) and its ability to control impulses emanating from the limbic system (the gas). Such findings provide a biological substrate to the argument that adolescents are less mature and lack the impulse control of mature adults.\textsuperscript{13-15} These findings show that the limbic system, responsible for emotions, matures before the prefrontal cortex, which is responsible for executive functioning. Furthermore, the tracts between the prefrontal cortex and the limbic system continue to be myelinated through adolescence.

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Metabolics

- Mean change in weight from baseline at end point for FANAPT patients was 2.1 kg across all short-term and long-term trials\textsuperscript{1}\n- The majority of patients taking FANAPT 24 mg/day did not experience a shift from normal to high in fasting lipid measurements in a 4-week study\textsuperscript{11}\n- Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics

Dosing flexibility

- Efficacy demonstrated at 6 mg twice daily, with dosing flexibility up to 12 mg twice daily\textsuperscript{1}

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*Based on pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies.
†Extrapyramidal symptoms.
‡ Percentage of patients who experienced weight gain of ≥7% of body weight was 12% for FANAPT 10-16 mg/day and 18% for FANAPT 20-24 mg/day versus 4% for placebo.
§3.6% of patients taking FANAPT 24 mg/day experienced a shift from normal (<200 mg/dL) to high (≥240 mg/dL) in fasting total cholesterol versus 1.4% of patients taking placebo. 10.1% of patients taking FANAPT 24 mg/day experienced a shift from normal (<150 mg/dL) to high (≥200 mg/dL) in fasting triglycerides versus 8.3% of patients taking placebo.

IMPORTANT SAFETY INFORMATION

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 atypical antipsychotic drugs have been shown to produce some metabolic changes, each drug in the class has its own specific risk profile.

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FANAPT\textsuperscript{®} (ioperidone) tablets

1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg
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ture than adults.
In a particular case, the strongest evidence for impulsivity usually comes from the details of the crime itself. If the crime can be shown to have occurred in the heat of the moment, as in the example given above, impulsivity is clear. If the crime is planned and predatory, the impulsivity argument may not apply. In some cases, historical data from collateral sources (such as reports of persons who know the defendant, previous mental health assessments and treatment, and prior criminal activities) may provide corroborative information regarding the defendant’s impulsivity in other situations.

Environmental circumstances
An adolescent typically has no choice in such matters as what neighborhood to live in; what school to attend; whom to live with; or whether he or she is able to continue to live in an impulsive, neglectful, or dangerous circumstance. Also, he is not responsible for the economic circumstances of his family. The Supreme Court has recognized this as a basis for decreased culpability: “[Adolescents’] own vulnerability and comparative lack of control over their immediate surroundings mean juveniles have a greater claim than adults to be forgiven for failing to escape negative influences in their whole environment.”17 There is strong statistical support linking adolescent crime rates to conditions of socioeconomic deprivation.18

Important Safety Information

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 compared to placebo-treated patients. A meta-analysis of placebo-controlled trials (median duration 10 weeks) largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients 1.6 to 1.9 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 cause of death was diverse, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infections (e.g., pneumonia) in nature. Observational studies using claims data similar to atypical antipsychotics drugs, treatment with conventional antipsychotics may increase mortality. The extent to which these findings of increased mortality in clinical studies may be attributed to the antipsychotic drug as opposed to some other characteristic(s) of the patients is not clear. FANAPT is not approved for the treatment of patients with dementia-related psychoses.

Contraindications: FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product. Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal syndrome, has been reported in association with administration of antipsychotic drugs. NMS can cause hyperpyrexia, muscle rigidity, altered mental status, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of the antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If antipsychotic treatment is considered to be a drug treatment after recovery from NMS, rechallenge must be carefully considered and patient should be carefully monitored.

Tardive Dyskinesia (TD): Risk of developing tardive dyskinesia, and the likelihood that it will become irreversible, may increase as the duration of treatment and the total cumulative dose increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment with low doses. Prescribing should be cautious. If TD occurs, discontinue treatment should be considered.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperlipidemia, dyslipidemia, and weight gain. All atypical antipsychotic drugs have been shown to produce some metabolic changes, each drug in the class has its own specific risk profile.
Ascertaining the socioeconomic background of a juvenile offender can often be done from collateral sources. Assessing the effect of adverse circumstances on an individual’s development is complex, but there is nevertheless considerable social science data on the effects of factors such as abuse, neglect, and family disruption that the expert may draw on to help justify his conclusions.

Peer group effects
If you want to know how much trouble an adolescent is getting into, ask how much trouble his friends are getting into. Most adolescent offending occurs in groups, and adolescents are especially vulnerable to peer pressure. Gang membership is one of the leading risk factors for predatory violence. Peer group effects are amplified in street subcultures, where it is necessary to appear tough to avoid being seen as weak and therefore vulnerable to attack. Such environments decrease responsibility when the violence, while considered wrong by society, is considered right in the subculture where a youth lives.

The details of the crime, particularly if the crime involved multiple perpetrators, provide evidence as to whether peer group effects were significant. In some cases, there may be characteristics in the defendant’s history that suggest susceptibility to peer pressure as well, such as when an intellectually disabled youth has a history of being easily talked into unwise actions by delinquent peers.
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Unfinished character development
We expect that a 15-year-old adolescent imprisoned for life will not be the same person at age 45; the same is not true for someone convicted as an adult whose personality is likely to remain relatively stable.

The fact that personality frequently changes from adolescence to adulthood has repeatedly been cited by the Supreme Court as one of the reasons why adolescents have lessened responsibility.1,3,4

Antisocial personality, by DSM convention, cannot be diagnosed until age 18. Psychopathy (a non-DSM convention), cannot be diagnosed until age 45, the Supreme Court as one of the reasons why adolescents have lessened responsibility.1,3,4

It is well established that among delinquent youths, the rate of mental disorders across the entire range of

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

5.5 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 (see Patient Counseling Information (17.3) in the full prescribing information). While all atypical antipsychotic drugs have been shown to produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoadiposis or hyperosmolar coma or death, has been reported in patients treated with antipsychotic including FANAPT. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the antipsychotics included in these studies. Because FANAPT was not marketed at the time these studies were performed, it is not known if FANAPT is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with 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 antidiabetic treatment despite discontinuation of the suspect drug.

Data from a 4-week, fixed-dose study in adult subjects with schizophrenia, in which fasting blood samples were drawn, in adult subjects with schizophrenia are presented in Table 3.

Table 1. Change in Fasting Glucose

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Placebo</th>
<th>FANAPT® 24 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td>n=114</td>
<td>n=226</td>
</tr>
<tr>
<td>Mean Change from Baseline</td>
<td>-0.5</td>
<td>6.6</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts</td>
<td>2.5%</td>
<td>(2/80)</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts (≥7% gain)</td>
<td>(1/80)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Change in Glucose

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Placebo</th>
<th>FANAPT® 10-16 mg/day</th>
<th>FANAPT® 20-24 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 months</td>
<td>-1.8 (N=723)</td>
<td>1.4 (N=80)</td>
<td></td>
</tr>
<tr>
<td>6-12 months</td>
<td>5.4 (N=723)</td>
<td>1.4 (N=80)</td>
<td></td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>5.4 (N=425)</td>
<td>1.4 (N=80)</td>
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</tbody>
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Table 3. Change in Fasting Lipids

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Placebo</th>
<th>FANAPT® 24 mg/day</th>
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</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>n=731</td>
<td>n=226</td>
</tr>
<tr>
<td>LDL</td>
<td>-2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>n=109</td>
<td>n=217</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>n=114</td>
<td>n=228</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>-3.5</td>
<td>0.5</td>
</tr>
<tr>
<td>n=114</td>
<td>n=228</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>16.47</td>
<td>-0.83</td>
</tr>
<tr>
<td>n=114</td>
<td>n=228</td>
<td></td>
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</table>

Table 3. Change in Fasting Lipids (cont)

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Placebo</th>
<th>FANAPT® 24 mg/day</th>
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</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>n=731</td>
<td>n=226</td>
</tr>
<tr>
<td>LDL</td>
<td>-2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>n=109</td>
<td>n=217</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>n=114</td>
<td>n=228</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>-3.5</td>
<td>0.5</td>
</tr>
<tr>
<td>n=114</td>
<td>n=228</td>
<td></td>
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<tr>
<td>Triglycerides</td>
<td>16.47</td>
<td>-0.83</td>
</tr>
<tr>
<td>n=114</td>
<td>n=228</td>
<td></td>
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</tbody>
</table>

Table 4: Change in Cholesterol

<table>
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<tr>
<th>Time Period</th>
<th>Placebo</th>
<th>FANAPT® 10-16 mg/day</th>
<th>FANAPT® 20-24 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 months</td>
<td>-3.9 (N=783)</td>
<td>-3.9 (N=728)</td>
<td>-7.7 (N=428)</td>
</tr>
<tr>
<td>6-12 months</td>
<td>-19.4 (N=234)</td>
<td>-23.2 (N=31)</td>
<td>-19.4 (N=20)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>-26.6 (N=24)</td>
<td>-35.4 (N=31)</td>
<td>-17.7 (N=20)</td>
</tr>
</tbody>
</table>

Table 5: Change in Triglycerides

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Placebo</th>
<th>FANAPT® 10-16 mg/day</th>
<th>FANAPT® 20-24 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 months</td>
<td>-8.9 (N=783)</td>
<td>-8.9 (N=728)</td>
<td>-7.7 (N=428)</td>
</tr>
<tr>
<td>6-12 months</td>
<td>-21.2 (N=35)</td>
<td>-21.2 (N=29)</td>
<td>-17.7 (N=20)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>-26.9 (N=24)</td>
<td>-35.4 (N=31)</td>
<td>-17.7 (N=20)</td>
</tr>
</tbody>
</table>

Table 6: Change in Body Weight

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Placebo</th>
<th>FANAPT® 10-16 mg/day</th>
<th>FANAPT® 20-24 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 months</td>
<td>-0.1</td>
<td>2.0</td>
<td>2.7</td>
</tr>
<tr>
<td>6-12 months</td>
<td>4%</td>
<td>12%</td>
<td>18%</td>
</tr>
</tbody>
</table>

5.6 Seizures
In short-term placebo-controlled trials (4– to 6-weeks), seizures occurred in 0.1% (1/1344) of patients treated with FANAPT compared to 0.3% (2/587) on placebo. As with other antipsychotics, FANAPT should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer’s dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.7 Orthostatic Hypotension and Syncope
FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. This reflects its alpha1-adrenergic antagonist properties. In double-blind placebo-controlled short-term studies, where the dose was increased slowly, as recommended above, syncope was reported in 0.4% (5/1344) of patients treated with FANAPT compared to 0.2% (1/587) on placebo. Orthostatic hypotension was reported in 2.4% (6/254) of patients given 20-24 mg/day, 2% of patients given 10-16 mg/day, and 1% of patients given placebo. More rapid titration would be expected to increase the rate of orthostatic hypotension and syncope.

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

5.8 Leukopenia, Neutropenia and Agranulocytosis
In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis (including fatal cases) has also been reported.
Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. In patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue FANAPT at the first sign of a decline in WBC in the absence of other causative factors. Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <0.5 x 10^9/L) should discontinue FANAPT and have their WBC followed until recovery.

5.9 Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, FANAPT elevates prolactin levels. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients.

Tissue culture experiments indicate that approximately one-third of human breast cancer cells are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Marked increases in serum prolactin were seen in mice and rats treated with FANAPT (see Nonclinical Laboratory Findings). 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; the available evidence is considered too limited to be conclusive at this time.

In a short-term placebo-controlled trial (4-weeks), the mean change from baseline to endpoint in prolactin levels for the FANAPT 24 mg/day-treated group was an increase of 2.6 ng/mL, compared to a decrease of 6.3 ng/mL in the placebo group. In this trial, elevated prolactin levels were observed in 26% of adults treated with FANAPT compared to 12% in the placebo group. In the short-term trials, FANAPT was associated with modest levels of prolactin elevation compared to greater prolactin elevations observed with some other antipsychotic agents. In pooled analysis from clinical studies including long-term trials, in 9210 adults treated with iloperidone, gynecomastia was reported in 2 male subjects (0.1%) compared to 0.2% in placebo-treated patients. In 2% of patients treated with FANAPT 20-24 mg/day, galactorrhea was reported in 8 female subjects (0.2%) compared to 3 female subjects (0.5%) in placebo-treated patients.

5.10 Body Temperature Regulation

Disruption of the body’s ability to reduce core body temperature has been observed with prolactin-elevating compounds. Long-standing hyperprolactinemia may increase the body’s ability to lower core body temperature, thereby increasing the risk of hypothermia, core temperature remains relatively stable even in cold environments. In patients treated with FANAPT, core body temperature remained relatively stable even in cold environments. In patients treated with FANAPT, core body temperature remained relatively stable even in cold environments.

5.11 Dystonia

Dystonic symptomatology and aspiration have been associated with antipsycho-....

5.12 Suicide

The possibility of a suicide attempt in individuals at risk for suicide.

5.13 Prispiram

Three cases of prispiram were reported in the pre-marketing FANAPT program. Drugs with alpha-adrenergic blocking effects have been reported to induce prispiram. FANAPT shares this pharmacologic activity. Severe prin...
The Adoleseent Brain

Adolescent brain is different, which carries with it an implication that we have to ward adults should not apply.

Conclusion

Assessments of partial culpability of adolescents are difficult in individual cases; however, the courts are moving away from mandatory sentencing to individual determinations, even for the most heinous crimes. These individual determinations can frequently be assisted by psychiatrists, because they have an ever-increasing database of behavior and neurobiological understanding on which to base their opinions.
Clinical Studies of FANAPT in the treatment of schizophrenia did not include safety and effectiveness in pediatric and adolescent patients. This population has not been studied extensively. A single 3 mg dose of iloperidone had no effect on the pharmacokinetics of dextromethorphan (80 mg dose) when a 3 mg dose of iloperidone was given, indicating that iloperidone is not a substrate for CYP2D6. Based on in vitro studies using human liver microsomes that showed that iloperidone does not have enzyme-inducing properties, specifically for the following cytochrome P450 isozymes: CYP2C9, CYP2C19, CYP3A4, CYP2C19, and CYP3A4. Dose range comparisons in which rats were given iloperidone at doses similar to the 1 mg/m² dose [MRHD] of 24 mg/kg/day on a mg/m² basis) of iloperidone orally during the period of organogenesis. The highest dose caused increased maternal food consumption and weight gain. Delayed skeletal ossification occurred at all doses. No teratogenic effects were seen. Delayed skeletal ossification, and an increased incidence of minor fetal skeletal anomalies and variations; this dose also caused decreased maternal food consumption and weight gain.

A study in mild and moderate liver impairment has not been conducted. FANAPT is not recommended for patients with hepatic impairment.

8.8 Smoking Status

Based on in vitro studies utilizing human liver enzymes, FANAPT is not a substrate for CYP2C9; smoking should therefore not have an effect on the pharmacokinetics of FANAPT.

10. OVERDOSAGE

10.1 Human Experience

In pre-marketing trials involving over 2,021 patients, accidental or intentional overdose of FANAPT was documented in eight patients ranging from 48 mg to 576 mg taken at once and 292 mg taken over a three-day period. No fatalities were reported from these cases. The largest confirmed single ingestion of FANAPT was 576 mg; no adverse physical effects were noted for this patient. The next largest confirmed ingestion of FANAPT was 438 mg over a four-day period; extrapyramidal symptoms and a QTc of 507 msec were reported for this patient with no cardiac sequelae. This patient resumed FANAPT treatment for an additional 11 months. In general, reported signs and symptoms were those resulting from an exaggeration of the known pharmacological effects (e.g., drooling and sedation, tachycardia and hypotension) of FANAPT.

10.2 Management of Overdose

There is no specific antitode for FANAPT. Therefore appropriate supportive measures should be instituted. In case of acute overdose, the physician should establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after initiation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias. If anticholinergic therapy is administered, diisopyramide, procarbazine and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of FANAPT. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of FANAPT, resulting in profound hypotension. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of FANAPT-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision should continue until the patient recovers.

16 STORAGE

Store FANAPT tablets at controlled room temperature, 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]. Protect FANAPT tablets from exposure to light and moisture. FANAPT® is a registered trademark of Vanda Pharmaceuticals Inc. and is used by Novartis Pharmaceuticals Corporation under license. Distributed by: Novartis Pharmaceuticals Corporation East Hanover, NJ 07936 T2012-42 January 2012

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