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(p835)]

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(pp569-570)] 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 negates 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,

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Table 1 Mental health issues in punishing adolescents

Purpose of punishment	Mental health issue
Retribution	Culpability
Incapacitation	Likelihood of recidivism
Rehabilitation	Amenability to treatment
Deterrence	Effect on thinking of potential offenders

Table 2 Factors to consider in assessing adolescent culpability[9]

- 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).[5] 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.[8] 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

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]*

INDICATION

FANAPT is an atypical antipsychotic agent indicated for the treatment of schizophrenia in adults. In choosing among treatments, prescribers should consider the ability of FANAPT to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate FANAPT slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration.

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. Analysis of seventeen placebo-controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the 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 (e.g., pneumonia) 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. FANAPT is not approved for the treatment of patients with dementia-related psychosis.

*Please see additional Important Safety Information and brief summary of Prescribing Information, including **Boxed WARNING,** on adjacent pages.*

and impulsivity. Cauffman and Steinberg[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.[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.[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 ma-

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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[1‡]
- 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[1§]

  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[1]

START YOUR PATIENTS ON FANAPT — FOR FREE.

FANAPT vouchers are good for 34 days (68 tablets) of FANAPT. Vouchers are available for download at **www.FANAPT.com**.

*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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Reference: 1. FANAPT [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; January 2012.

NOVARTIS

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Fanapt® (iloperidone) 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 to continue to live in abusive, neglectful, or dangerous circumstances. 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."[3] There is strong statistical support linking adolescent crime rates to conditions of socioeconomic deprivation.[16]

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. Analysis of seventeen placebo-controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the 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 (e.g., pneumonia) 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. FANAPT is not approved for the treatment of patients with dementia-related psychosis.

Contraindications: FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product.

Cerebrovascular Adverse Events, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. FANAPT is not approved for treatment of patients with dementia-related psychosis.

QT Prolongation: FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (e.g., paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec. No cases of torsades de pointes or other severe cardiac arrhythmias were observed during the premarketing clinical program. FANAPT should be avoided in combination with other drugs that are known to prolong QTc. FANAPT should also be avoided in patients with congenital long QT syndrome and in patients with history of cardiac arrhythmias, and in circumstances that may increase risk of torsades de pointes and/or sudden death in association with use of drugs that prolong the QTc interval. Use caution and consider dose modification. Patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, 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 dysarrhythmia. 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 required after recovery from NMS, reintroduction should 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 periods at low doses. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, drug discontinuation should be considered.

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 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: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including FANAPT. Patients with an established diagnosis of, or with risk factors for, diabetes mellitus 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 be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment 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 antipsychotic.

Dyslipidemia: Undesirable alterations in lipids 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.

Seizures: As with other antipsychotics, FANAPT should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold, e.g., Alzheimer's dementia.

Orthostatic Hypotension and Syncope: FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. Therefore FANAPT must be titrated as directed. FANAPT should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose the patient to hypotension. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: In clinical trial and postmarketing experience with antipsychotic agents, events of leukopenia/neutropenia have been reported temporally. Agranulocytosis (including death) has also been reported. Patients with a preexisting low white blood cell count 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.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, FANAPT elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds.

Body Temperature Regulation: Appropriate care is advised when prescribing FANAPT for 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.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. FANAPT and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for FANAPT should be written for the smallest quantity of tablets in order to reduce the risk of overdose.

Priapism: Three cases of priapism have been reported in the premarketing FANAPT program. Severe priapism may require surgical intervention.

Cognitive and Motor Impairment: FANAPT, like other antipsychotics, has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with FANAPT does not affect them adversely.

Commonly observed adverse events: Commonly observed adverse reactions (incidence ≥5% and twofold greater than placebo) were: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increase.

Specific Populations

Pregnancy: FANAPT is Pregnancy Category C.

Hepatic Impairment: FANAPT is not recommended for patients with hepatic impairment.

Drug Interactions: Given the primary CNS effects of FANAPT, caution should be used when it is taken in combination with other centrally acting drugs and alcohol. FANAPT has the potential to enhance the effect of certain antihypertensive agents. Coadministration of FANAPT with potential CYP2D6 inhibitors (e.g., fluoxetine, paroxetine) and potential CYP3A4 inhibitors (e.g., ketoconazole) should be done with caution. FANAPT dose should be reduced by one-half. Cautiously approach coadministration of drugs mainly eliminated via CYP3A4 with FANAPT.

Please see brief summary of Prescribing Information, including ***Boxed WARNING****, on adjacent pages.*

Ascertaining the socioeconomic background of a juvenile offender can often be done from collateral sources. Assessing the effect of adverse circumstances on an individual defendant is more 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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FANAPT® (iloperidone) tablets
Initial U.S. Approval: 2009

BRIEF SUMMARY: Please see package insert for full prescribing 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. Analysis of seventeen placebo-controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the 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 (e.g., pneumonia) 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. FANAPT is not approved for the treatment of patients with Dementia-Related Psychosis. [see Warnings and Precautions (5.1)]

1 INDICATIONS AND USAGE

FANAPT® tablets are indicated for the treatment of adults with schizophrenia. Efficacy was established in two short-term (4- and 6-week) placebo- and active-controlled studies of adult patients with schizophrenia *[see Clinical Studies (14) in the full prescribing information]*.

When deciding among the alternative treatments available for this condition, the prescriber should consider the finding that FANAPT is associated with prolongation of the QTc interval *[see Warnings and Precautions (5.2)]*. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia which can result in sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether FANAPT will cause torsade de pointes or increase the rate of sudden death is not yet known.

Patients must be titrated to an effective dose of FANAPT. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to some other antipsychotic drugs that do not require a similar titration. Prescribers should be mindful of this delay when selecting an antipsychotic drug for the treatment of schizophrenia *[see Dosage and Administration (2.1) and Clinical Studies (14) in the full prescribing information]*.

The effectiveness of FANAPT in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use FANAPT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2.3) in the full prescribing information]*.

4 CONTRAINDICATIONS

FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product. Reactions have included pruritus and urticaria.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risks in Elderly Patients with Dementia-Related Psychosis Increased Mortality

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. FANAPT is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

Cerebrovascular Adverse Events, Including Stroke

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. FANAPT is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

5.2 QT Prolongation

In an open-label QTc study in patients with schizophrenia or schizoaffective disorder (n=160), FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec.

No cases of torsade de pointes or other severe cardiac arrhythmias were observed during the pre-marketing clinical program.

The use of FANAPT 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 (e.g., pentamidine, levomethadyl acetate, methadone). FANAPT 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 torsade 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 prolongation of the QT interval; (5) recent acute myocardial infarction; and/or (6) uncompensated heart failure.

Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism *[see Drug Interactions (7.1)]*, and in patients with reduced activity of CYP2D6 *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

It is recommended that patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. FANAPT should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 ms.

If patients taking FANAPT experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) 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 (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of this syndrome should include: (1) immediate discontinuation of the antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, which may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely on prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to 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 are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic administered increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, FANAPT 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 (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. 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.

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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 diagnosis, but one used in forensic psychiatry to get at the more internal aspects of antisocial personality, such as exploitativeness and severe deficits in empathy and guilt) is an especially worrisome personality type when seen in adolescents. Nevertheless, psychopathy diagnosed in adolescence is not highly predictive of adult psychopathy: the reported correlation of $r = 0.31$, while significant, is not strong enough to account for enough of the variance to be very useful in sentencing an individual delinquent.[17] In addition to the clinical interview, a variety of personality tests can be used to buttress conclusions about the defendant's present personality characteristics.

Mental illness

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 ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics 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 atypical 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 be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment 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, are presented in Table 1.

Table 1. Change in Fasting Glucose

	Placebo	FANAPT® 24 mg/day
	Mean Change from Baseline (mg/dL)	
	n=114	n=228
Serum Glucose Change from Baseline	-0.5	6.6
	Proportion of Patients with Shifts	
Serum Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	2.5% (2/80)	10.7% (18/169)

Pooled analyses of glucose data from clinical studies including longer term trials are shown in Table 2.

Table 2: Change in Glucose

	Mean Change from Baseline (mg/dL)		
	3-6 months	6-12 months	>12 months
FANAPT 10-16 mg/day	1.8 (N=773)	5.4 (N=723)	5.4 (N=425)
FANAPT 20-24 mg/day	-3.6 (N=34)	-9.0 (N=31)	-18.0 (N=20)

Dyslipidemia

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

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

Table 3. Change in Fasting Lipids

	Placebo	FANAPT® 24 mg/day
	Mean Change from Baseline (mg/dL)	
Cholesterol	n=114	n=228
Change from baseline	-2.17	8.18
LDL	n= 109	n=217
Change from baseline	-1.41	9.03
HDL	n= 114	n=228
Change from baseline	-3.35	0.55
Triglycerides	n= 114	n=228
Change from baseline	16.47	-0.83

(continued)

Table 3. Change in Fasting Lipids (cont)

	Placebo	FANAPT® 24 mg/day
	Proportion of Patients with Shifts	
Cholesterol		
Normal to High (<200 mg/dL to ≥240 mg/dL)	1.4% (1/72)	3.6% (5/141)
LDL		
Normal to High (<100 mg/dL to ≥160 mg/dL)	2.4% (1/42)	1.1% (1/90)
HDL		
Normal to Low (≥40 mg/dL to <40 mg/dL)	23.8% (19/80)	12.1% (20/166)
Triglycerides		
Normal to High (<150 mg/dL to ≥200 mg/dL)	8.3% (6/72)	10.1% (15/148)

Pooled analyses of cholesterol and triglyceride data from clinical studies including longer term trials are shown in Tables 4 and 5.

Table 4: Change in Cholesterol

	Mean Change from Baseline (mg/dL)		
	3-6 months	6-12 months	>12 months
FANAPT 10-16 mg/day	-3.9 (N=783)	-3.9 (N=726)	-7.7 (N=428)
FANAPT 20-24 mg/day	-19.4 (N=34)	-23.2 (N=31)	-19.4 (N=20)

Table 5: Change in Triglycerides

	Mean Change from Baseline (mg/dL)		
	3-6 months	6-12 months	>12 months
FANAPT 10-16 mg/day	-8.9 (N=783)	-8.9 (N=726)	-17.7 (N=428)
FANAPT 20-24 mg/day	-26.6 (N=34)	-35.4 (N=31)	-17.7 (N=20)

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Across all short- and long-term studies, the overall mean change from baseline at endpoint was 2.1 kg.

Changes in body weight (kg) and the proportion of subjects with ≥7% gain in body weight from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in adult subjects are presented in Table 6.

Table 6. Change in Body Weight

	Placebo	FANAPT 10-16 mg/day	FANAPT 20-24 mg/day
	n=576	n=481	n=391
Weight (kg) Change from Baseline	-0.1	2.0	2.7
Weight Gain ≥7% increase from Baseline	4%	12%	18%

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 with 0.2% (1/587) on placebo. Orthostatic hypotension was reported in 5% of patients given 20-24 mg/day, 3% 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.

diagnoses is high.[18,19] Excluding conduct disorders, more than 60% of incarcerated juveniles report at least one disorder, about triple the rate in the general population, and more than 40% report more than one disorder. In most cases, delinquent behavior is not thought to be "caused" by mental illness, but a mental disorder likely magnifies the effects of other factors relevant to reducing culpability through such pathways as further impairing judgment and slowing consolidation of a healthy identity. When an evaluation reveals a mental illness, the youth's amenability to treatment has implications for rehabilitation.

Attitudes toward adolescence

Attitudes toward juvenile offending range from "do the crime, do the time," with its implication for full adult punishment, to "they're just kids"—a response that elicits more parental feelings of helping offenders not repeat their problematic behavior. Reacting to adolescents as though they are adults brings with it the ready set of attitudes that we apply to adult offenders. If we see adolescents as different from adults, but also as different from children, then we will use, or have to find, a different set of attitudes.

Attorneys often ask experts to testify "about the adolescent brain" in sentencing hearings. Why does such testimony have power? The data showing that adolescents are more impulsive come from studies of behavior, not imaging studies. But the neuroimaging data indicate that the

(Please see The Adolescent Brain, *page 32)*

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. 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 <1000/mm^3) 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 gonadalsteroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, 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 cancers 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. Mammary gland proliferative changes and increases in serum prolactin were seen in mice and rats treated with FANAPT *[see Nonclinical Toxicology (13.1) in the 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; 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 plasma 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 plasma 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 longer term trials, in 3210 adults treated with iloperidone, gynecomastia was reported in 2 male subjects (0.1%) compared to 0% in placebo-treated patients, and 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 attributed to antipsychotic agents. Appropriate care is advised when prescribing FANAPT for 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.

5.11 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. FANAPT and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see Boxed Warning]*.

5.12 Suicide

The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for FANAPT should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

5.13 Priapism

Three cases of priapism were reported in the pre-marketing FANAPT program. Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. FANAPT shares this pharmacologic activity. Severe priapism may require surgical intervention.

5.14 Potential for Cognitive and Motor Impairment

FANAPT, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. In short-term, placebo-controlled trials, somnolence (including sedation) was reported in 11.9% (104/874) of adult patients treated with FANAPT at doses of 10 mg/day or greater versus 5.3% (31/587) treated with placebo. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with FANAPT does not affect them adversely.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial 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. The information below is derived from a clinical trial database for FANAPT consisting of 2070 patients exposed to FANAPT at doses of 10 mg/day or greater, for the treatment of schizophrenia. All of these patients who received FANAPT were participating in multiple-dose clinical trials. The conditions and duration of treatment with FANAPT varied greatly and included (in overlapping categories), open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose studies, and short-term and longer-term exposure.

Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions, reactions were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse reactions represent the proportions of individuals who experienced a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The information presented in these sections was derived from pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in patients who received FANAPT at daily doses within a range of 10 to 24 mg (n=874).

Adverse Reactions Occurring at an Incidence of 2% or More among FANAPT-Treated Patients and More Frequent than Placebo

Table 7 enumerates the pooled incidences of treatment-emergent adverse reactions that were spontaneously reported in four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, listing those reactions that occurred in 2% or more of patients treated with FANAPT in any of the dose groups, and for which the incidence in FANAPT-treated patients in any dose group was greater than the incidence in patients treated with placebo.

Table 7: Treatment-Emergent Adverse Reactions in Short-Term, Fixed- or Flexible-Dose, Placebo-Controlled Trials in Adult Patients*

Body System or Organ Class Dictionary-derived Term	Percentage of Patients Reporting Reaction Placebo (N=587)	 FANAPT 10-16 mg/day (N=483)	 FANAPT 20-24 mg/day (N=391)
Body as a Whole			
Arthralgia	2	3	3
Fatigue	3	4	6
Musculoskeletal Stiffness	1	1	3
Weight Increased	1	1	9
Cardiac Disorders			
Tachycardia	1	3	12
Eye Disorders			
Vision Blurred	2	3	1
Gastrointestinal Disorders			
Nausea	8	7	10
Dry Mouth	1	8	10
Diarrhea	4	5	7
Abdominal Discomfort	1	1	3
Infections			
Nasopharyngitis	3	4	3
Upper Respiratory Tract Infection	1	2	3
Nervous System Disorders			
Dizziness	7	10	20
Somnolence	5	9	15
Extrapyramidal Disorder	4	5	4
Tremor	2	3	3
Lethargy	1	3	1
Reproductive System			
Ejaculation Failure	<1	2	2
Respiratory			
Nasal Congestion	2	5	8
Dyspnea	<1	2	2
Skin			
Rash	2	3	2
Vascular Disorders			
Orthostatic Hypotension	1	3	5
Hypotension	<1	<1	3

*Table includes adverse reactions that were reported in 2% or more of patients in any of the FANAPT dose groups and which occurred at greater incidence than in the placebo group. Figures rounded to the nearest integer.

Dose-Related Adverse Reactions in Clinical Trials

Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, adverse reactions that occurred with a greater than 2% incidence in the patients treated with FANAPT, and for which the incidence in patients treated with FANAPT 20-24 mg/day were twice than the incidence in patients treated with FANAPT 10-16 mg/day were: abdominal discomfort, dizziness, hypotension, musculoskeletal stiffness, tachycardia, and weight increased.

Common and Drug-Related Adverse Reactions in Clinical Trials

Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, the following adverse reactions occurred in ≥5% incidence in the patients treated with FANAPT and at least twice the placebo rate for at least one dose: dizziness, dry mouth, fatigue, nasal congestion,

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adolescent brain is different, which carries with it an implication that the reactive attitudes that we have toward 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 behavioral and neurobiological understanding on which to base their opinions.

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References

1. *Miller v Alabama,* 567 US (2012).
2. *Thompson v Oklahoma,* 487 US 815 (1988).
3. *Roper v Simmons,* 543 US 551; 2005.
4. *Graham v Florida,* 560 US, 130 S.Ct. 2011, (2010).
5. Elliott DS. Serious violent offenders: onset, developmental course, and termination: The American Society of Criminology 1993 Presidential Address. *Criminology.* 1994;32:1-22.
6. Office of the Surgeon General. *Youth Violence: A Report of the Surgeon General.* Rockville, MD: US Public Health Service, Office of the Surgeon General; 2001.
7. Monahan KC, Steinberg L, Cauffman E, Mulvey EP. Trajectories of antisocial behavior and psychosocial maturity from adolescence to young adulthood. *Dev*

somnolence, tachycardia, orthostatic hypotension, and weight increased. Dizziness, tachycardia, and weight increased were at least twice as common on 20-24 mg/day as on 10-16 mg/day.

Extrapyramidal Symptoms (EPS) in Clinical Trials
Pooled data from the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies provided information regarding treatment-emergent EPS. Adverse event data collected from those trials showed the following rates of EPS-related adverse events as shown in Table 8.

Table 8: Percentage of EPS Compared to Placebo

Adverse Event Term	Placebo (%) (N=587)	FANAPT 10-16 mg/day (%) (N=483)	FANAPT 20-24 mg/day (%) (N=391)
All EPS events	**11.6**	**13.5**	**15.1**
Akathisia	2.7	1.7	2.3
Bradykinesia	0	0.6	0.5
Dyskinesia	1.5	1.7	1.0
Dystonia	0.7	1.0	0.8
Parkinsonism	0	0.2	0.3
Tremor	1.9	2.5	3.1

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials
Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, there was no difference in the incidence of discontinuation due to adverse events between FANAPT-treated (5%) and placebo-treated (5%) patients. The types of adverse events that led to discontinuation were similar for the FANAPT- and placebo-treated patients.

Demographic Differences in Adverse Reactions in Clinical Trials
An examination of population subgroups in the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies did not reveal any evidence of differences in safety on the basis of age, gender or race *[see Warnings and Precautions (5.1)]*.

Laboratory Test Abnormalities in Clinical Trials
There were no differences between FANAPT and placebo in the incidence of discontinuation due to changes in hematology, urinalysis, or serum chemistry.

In short-term placebo-controlled trials (4- to 6-weeks), there were 1.0% (13/1342) iloperidone-treated patients with hematocrit at least one time below the extended normal range during post-randomization treatment, compared to 0.3% (2/585) on placebo. The extended normal range for lowered hematocrit was defined in each of these trials as the value 15% below the normal range for the centralized laboratory that was used in the trial.

Other Reactions During the Pre-marketing Evaluation of FANAPT
The following is a list of MedDRA terms that reflect treatment-emergent adverse reactions in patients treated with FANAPT at multiple doses ≥4 mg/day during any phase of a trial with the database of 3210 FANAPT-treated patients. All reported reactions are included except those already listed in Table 7, or other parts of the *Adverse Reactions (6)* section, those considered in the *Warnings and Precautions (5)*, those reaction terms which were so general as to be uninformative, reactions reported in fewer than 3 patients and which were neither serious nor life-threatening, reactions that are otherwise common as background reactions, and reactions considered unlikely to be drug related. It is important to emphasize that, although the reactions reported occurred during treatment with FANAPT, they were not necessarily caused by it.

Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not listed in Table 7 appear in this listing); infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic Disorders: Infrequent – anemia, iron deficiency anemia; *Rare* – leukopenia

Cardiac Disorders: Frequent – palpitations; *Rare* – arrhythmia, atrioventricular block first degree, cardiac failure (including congestive and acute)

Ear and Labyrinth Disorders: Infrequent – vertigo, tinnitus

Endocrine Disorders: Infrequent – hypothyroidism

Eye Disorders: Frequent – conjunctivitis (including allergic); *Infrequent* – dry eye, blepharitis, eyelid edema, eye swelling, lenticular opacities, cataract, hyperemia (including conjunctival)

Gastrointestinal Disorders: Infrequent – gastritis, salivary hypersecretion, fecal incontinence, mouth ulceration; *Rare* – aphthous stomatitis, duodenal ulcer, hiatus hernia, hyperchlorhydria, lip ulceration, reflux esophagitis, stomatitis

General Disorders and Administrative Site Conditions: Infrequent – edema (general, pitting, due to cardiac disease), difficulty in walking, thirst; *Rare* – hyperthermia

Hepatobiliary Disorders: Infrequent – cholelithiasis

Investigations: Frequent: weight decreased; *Infrequent* – hemoglobin decreased, neutrophil count increased, hematocrit decreased

Metabolism and Nutrition Disorders: Infrequent – increased appetite, dehydration, hypokalemia, fluid retention

Musculoskeletal and Connective Tissue Disorders: Frequent – myalgia, muscle spasms; *Rare* – torticollis

Nervous System Disorders: Infrequent – paresthesia, psychomotor hyperactivity, restlessness, amnesia, nystagmus; *Rare* – restless legs syndrome

Psychiatric Disorders: Frequent – restlessness, aggression, delusion; *Infrequent* – hostility, libido decreased, paranoia, anorgasmia, confusional state, mania, catatonia, mood swings, panic attack, obsessive-compulsive disorder, bulimia nervosa, delirium, polydipsia psychogenic, impulse-control disorder, major depression

Renal and Urinary Disorders: Frequent – urinary incontinence; *Infrequent* – dysuria, pollakiuria, enuresis, nephrolithiasis; *Rare* – urinary retention, renal failure acute

Reproductive System and Breast Disorders: Frequent – erectile dysfunction; *Infrequent* – testicular pain, amenorrhea, breast pain; *Rare* – menstruation irregular, gynecomastia, menorrhagia, metrorrhagia, postmenopausal hemorrhage, prostatitis.

Respiratory, Thoracic and Mediastinal Disorders: Infrequent – epistaxis, asthma, rhinorrhea, sinus congestion, nasal dryness; *Rare* – dry throat, sleep apnea syndrome, dyspnea exertional

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Fanapt: retrograde ejaculation. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS
Given the primary CNS effects of FANAPT, caution should be used when it is taken in combination with other centrally acting drugs and alcohol. Due to its α1-adrenergic receptor antagonism, FANAPT has the potential to enhance the effect of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect FANAPT
Iloperidone is not a substrate for CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. This suggests that an interaction of iloperidone with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for iloperidone metabolism. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., fluoxetine, paroxetine) can inhibit iloperidone elimination and cause increased blood levels.

Ketoconazole: Co-administration of ketoconazole (200 mg twice daily for 4 days), a potent inhibitor of CYP3A4, with a 3 mg single dose of iloperidone to 19 healthy volunteers, ages 18-45, increased the AUC of iloperidone and its metabolites P88 and P95 by 57%, 55% and 35%, respectively. Iloperidone doses should be reduced by about one-half when administered with ketoconazole or other strong inhibitors of CYP3A4 (e.g., itraconazole). Weaker inhibitors (e.g., erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level.

Fluoxetine: Co-administration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 29-44, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2-3 fold, and decreased the AUC of its metabolite P95 by one-half. Iloperidone doses should be reduced by one-half when administered with fluoxetine. When fluoxetine is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level. Other strong inhibitors of CYP2D6 would be expected to have similar effects and would need appropriate dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to the previous level.

Paroxetine: Co-administration of paroxetine (20 mg/day for 5-8 days), a potent inhibitor of CYP2D6, with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 resulted in increased mean steady-state peak concentrations of iloperidone and its metabolite P88, by about 1.6 fold, and decreased mean steady-state peak concentrations of its metabolite P95 by one-half. Iloperidone doses should be reduced by one-half when administered with paroxetine. When paroxetine is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level. Other strong inhibitors of CYP2D6 would be expected to have similar effects and would need appropriate dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to previous levels.

Paroxetine and Ketoconazole: Co-administration of paroxetine (20 mg once daily for 10 days), a CYP2D6 inhibitor, and ketoconazole (200 mg twice daily) with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 resulted in a 1.4 fold increase in steady-state concentrations of iloperidone and its metabolite P88 and a 1.4 fold decrease in the P95 in the presence of paroxetine. So giving iloperidone with inhibitors of both of its metabolic pathways did not add to the effect of either inhibitor given alone. Iloperidone doses should therefore be reduced by about one-half if administered concomitantly with both a CYP2D6 and CYP3A4 inhibitor.

7.2 Potential for FANAPT to Affect Other Drugs
In vitro studies in human liver microsomes showed that iloperidone does not substantially inhibit the metabolism of drugs metabolized by the following cytochrome P450 isozymes: CYP1A1, CYP1A2, CYP2A6, CYP2B6,

Psychol. 2009;45:1654-1668.
8. Zimring FE. Penal proportionality for the young offender: notes on immaturity, capacity, and diminished responsibility. In: Grisso T, Schwartz RG, eds. *Youth on Trial: A Developmental Perspective on Juvenile Justice*. Chicago: University of Chicago Press; 2000:271-289.
9. Ash P. But he knew it was wrong: evaluating adolescent culpability. *J Am Acad Psychiatry Law.* 2012;40:21-32.
10. Cauffman E, Steinberg L. (Im)maturity of judgment in adolescence: why adolescents may be less culpable than adults. *Behav Sci Law.* 2000;18:741-760.
11. American Medical Association, American Academy of Child and Adolescent Psychiatry. *Brief for the American Medical Association and American Academy of Child and Adolescent Psychiatry as Amici Curiae in Support of Neither Party, in* Miller v. Alabama, *US Supreme Court Cases Nos. 10-9646, 10-9647*; 2012.
12. American Psychological Association. *Brief of the American Psychological Association, American Psychiatric Association, National Association of Social Workers, and Mental Health America as Amici Curiae Supporting Petitioners, in* Graham v. Florida *and* Sullivan v. Florida, *US Supreme Court Case Nos. 08-7412 and 08-7621;* 2009.
13. Giedd JN. The teen brain: insights from neuroimaging. *J Adolesc Health.* 2008;42:335-343.
14. Johnson SB, Blum RW, Giedd JN. Adolescent maturity and the brain: the promise and pitfalls of neuroscience research in adolescent health policy. *J Adolesc Health.* 2009;45:216-221.
15. Raznahan A, Shaw P, Lalonde F, et al. How does your cortex grow? *J Neurosci.* 2011;31:7174-7177.
16. Fagan J. Contexts of choice by adolescents in criminal events. In: Grisso T, Schwartz RG, eds. *Youth on Trial: A Developmental Perspective on Juvenile Justice*. Chicago: University of Chicago Press; 2000:371-401.
17. Lynam DR, Caspi A, Moffitt TE, et al. Longitudinal evidence that psychopathy scores in early adolescence predict adult psychopathy. *J Abnorm Psychol.* 2007;116:155-165.
18. Marsteller FA, Brogan D, Smith I, et al. *The Prevalence of Psychiatric Disorders Among Juveniles Admitted to Department of Children and Youth Services Regional Youth Detention Centers: Technical Report.* Atlanta: Georgia Dept of Juvenile Justice; 1997.
19. Teplin LA, Abram KM, McClelland GM, et al. Psychiatric disorders in youth in juvenile detention. *Arch Gen Psychiatry.* 2002;59:1133-1143. ❐

CYP2C8, CYP2C9, or CYP2E1. Furthermore, *in vitro* studies in human liver microsomes showed that iloperidone does not have enzyme inducing properties, specifically for the following cytochrome P450 isozymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5.

Dextromethorphan: A study in healthy volunteers showed that changes in the pharmacokinetics of dextromethorphan (80 mg dose) when a 3 mg dose of iloperidone was co-administered resulted in a 17% increase in total exposure and a 26% increase in C_{max} of dextromethorphan. Thus, an interaction between iloperidone and other CYP2D6 substrates is unlikely.

Fluoxetine: A single 3 mg dose of iloperidone had no effect on the pharmacokinetics of fluoxetine (20 mg twice daily).

7.3 Drugs that Prolong the QT Interval
FANAPT should not be used with any other drugs that prolong the QT interval *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C

FANAPT caused developmental toxicity, but was not teratogenic, in rats and rabbits.

In an embryo-fetal development study, pregnant rats were given 4, 16, or 64 mg/kg/day (1.6, 6.5, and 26 times the maximum recommended human dose [MRHD] of 24 mg/day on a mg/m^2 basis) of iloperidone orally during the period of organogenesis. The highest dose caused increased early intrauterine deaths, decreased fetal weight and length, decreased fetal skeletal ossification, and an increased incidence of minor fetal skeletal anomalies and variations; this dose also caused decreased maternal food consumption and weight gain.

In an embryo-fetal development study, pregnant rabbits were given 4, 10, or 25 mg/kg/day (3, 8, and 20 times the MRHD on a mg/m^2 basis) of iloperidone during the period of organogenesis. The highest dose caused increased early intrauterine deaths and decreased fetal viability at term; this dose also caused maternal toxicity.

In additional studies in which rats were given iloperidone at doses similar to the above beginning from either pre-conception or from day 17 of gestation and continuing through weaning, adverse reproductive effects included prolonged pregnancy and parturition, increased stillbirth rates, increased incidence of fetal visceral variations, decreased fetal and pup weights, and decreased post-partum pup survival. There were no drug effects on the neurobehavioral or reproductive development of the surviving pups. No-effect doses ranged from 4 to 12 mg/kg except for the increase in stillbirth rates which occurred at the lowest dose tested of 4 mg/kg, which is 1.6 times the MRHD on a mg/m^2 basis. Maternal toxicity was seen at the higher doses in these studies.

The iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present in significant amounts in rats, was given to pregnant rats during the period of organogenesis at oral doses of 20, 80, or 200 mg/kg/day. No teratogenic effects were seen. Delayed skeletal ossification occurred at all doses. No significant maternal toxicity was produced. Plasma levels of P95 (AUC) at the highest dose tested were 2 times those in humans receiving the MRHD of iloperidone.

There are no adequate and well-controlled studies in pregnant women.

Non-Teratogenic Effects
Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

FANAPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery
The effect of FANAPT on labor and delivery in humans is unknown.

8.3 Nursing Mothers
FANAPT was excreted in milk of rats during lactation. It is not known whether FANAPT or its metabolites are excreted in human milk. It is recommended that women receiving FANAPT should not breast feed.

8.4 Pediatric Use
Safety and effectiveness in pediatric and adolescent patients have not been established.

8.5 Geriatric Use
Clinical Studies of FANAPT in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 years and over to determine whether or not they respond differently than younger adult patients. Of the 3210 patients treated with FANAPT in pre-marketing trials, 25 (0.5%) were ≥65 years old and there were no patients ≥75 years old.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile (i.e., increased risk in mortality and cerebrovascular events including stroke) in this population compared to younger patients with schizophrenia *[see Boxed Warning and Warnings and Precautions (5.1)]*. The safety and efficacy of FANAPT in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with FANAPT, vigilance should be exercised.

8.6 Renal Impairment
Because FANAPT is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a significant impact on the pharmacokinetics of FANAPT. Renal impairment (creatinine clearance <30 mL/min) had minimal effect on maximum plasma concentrations (C_{max}) of iloperidone (given in a single dose of 3 mg) and its metabolites P88 and P95 in any of the three analytes measured. $AUC_{0-\infty}$ was increased by 24%, decreased by 6%, and increased by 52% for iloperidone, P88 and P95, respectively, in subjects with renal impairment.

8.7 Hepatic Impairment
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 CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of FANAPT.

10 OVERDOSAGE

10.1 Human Experience
In pre-marketing trials involving over 3210 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 interval 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., drowsiness and sedation, tachycardia and hypotension) of FANAPT.

10.2 Management of Overdose
There is no specific antidote 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 intubation, 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 antiarrhythmic therapy is administered, disopyramide, procainamide 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 problematic 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.

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