Don't Miss Underlying Adoption-Related Grief

BY MITCHEL L. ZOLER

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY

NEW YORK – Adoption is founded on loss, and a child's reaction to being adopted often can be best understood with a grief model.

The unresolved, uncommunicated, and unvalidated grief that some adopted children may feel often goes unrecognized as an overlay that accompanies more typical psychiatric disorders in adopted children, David Brodzinsky, Ph.D., said at the meeting.

In other cases, adopted children might act up and present what looks like a serious psychiatric problem, but closer examination shows it is an adjustment reaction or other low-level problem that occurs as an adopted child struggles to understand the meaning and implications of adoption, said Dr. Brodzinsky, research and project director at the Evan B. Donaldson Adoption Institute in Oakland, Calif.

"I see two kinds of cases. In children with clinically relevant problems, such as depression, anxiety, or attention-deficit/hyperactivity disorder, the grief model is secondary to understanding and dealing with the psychopathology they have. But there is an overlay that often gets missed, a sense of loss that often is not treated because what you see is depression or anxiety, and that has to be dealt with first. But we need to be sure not to miss the underlying sense of grief and loss. It's not always present, but we need to look for it, and when it's present, it needs to be dealt with," Dr. Brodzinsky said in an interview.

The second type of case involves chil-

Table 3: Change in Lipids Compared to Placebo

Mean change from baseline (mg/dL)	Placebo (N=587)	FANAPT 10-16 mg/day (N=483)	FANAPT 20-24 mg/day (N=391)
Triglycerides	-26.5	-26.5	-8.8
Total Cholesterol	-7.7	-3.9	3.9

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 1, 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 1 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 – anaemia, 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 – paraesthesia, 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

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, 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)]*.

dren who have what might appear to be depression or anxiety but rather are symptoms that result exclusively from adoption-related grief that has not been appropriately validated.

However, the vast majority of adopted kids do not experience unvalidated grief and are "well within the normal range and do quite well," he said. "Adopted individuals are highly variable in the way they experience adoption-related loss."

If a sense of loss occurs among children who were adopted as infants, it usually appears before age 5-7 years. Children can begin to have a feeling of separation from someone about whom they don't know much, which can lead to anxiety, sadness, and anger. In some children, "the experience of loss may be quite subtle and not easily observed by others."

Children who were adopted at an older age are more likely to have a more traumatic reaction, but again their understanding of adoption and their reaction to it varies over time as they age. "As children begin to understand the implications of their adoptive status, they become increasingly sensitized to adoption-related loss," Dr. Brodzinsky said.

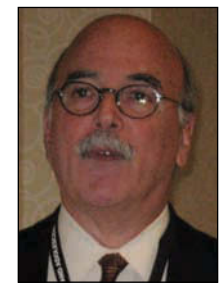
The sense of loss that some adopted children develop can stem from several different factors and realizations, including loss of birth parents and loss of their entire birth family; loss of their biological, ethnic, racial, and cultural origins; loss of prior nonbiological caregivers; loss of status among their peers; loss of their emotional stability; loss of their feeling of fitting in with their adoptive family; loss of privacy; and loss of their self-identify.

Perhaps the most important consequence of an emerging sense of loss occurs when it leads to disenfranchised grief: The loss goes unrecognized by others or is minimized or trivialized. "Too often, the focus in adoption is on what the child gained" without an acknowledgment of what was lost, he said. "Too often adoptees and birth parents have not had their sense of loss validated by people around them."

Adopted children face the risk that their blocked, disenfranchised grief could become clinical depression. Viewing the loss in a grief model normalizes the child's reactions rather than casting them as pathological.

Four interventions have shown efficacy for resolving grief and a sense of loss in adopted children. Two approaches especially suited to younger children are "life books" and bibliotherapy. Therapeutic rituals can help at any age. Written role play is a good intervention for older teens and adults.

Many therapists use life books for interventions. Dr. Brodzinsky prefers books created by the patient, often as loose-leaf pages in a binder, rather than commercially available versions. The book is like a photo album of the child's past, but can also contain drawings and text. The child constructs the book, which helps bring order to what can feel like an otherwise chaotic life story, giving the child a sense of where she comes from and where she is going. What goes into the book depends on the child's age, willingness to deal with various adoption issues, and the information available.



Therapeutic rituals can be effective for a child of any age if rituals are part of a family's life.

DR. BRODZINSKY

When used in treatment, the child and therapist review the contents of the book repeatedly, as well as adding to it when appropriate. Use of a book opens communication, gives the child a more realistic understanding of his adoption, and gives the child a more positive view of self. Life books usually work best for those aged 4 years to about 11, Dr. Brodzinsky said.

Bibliotherapy involves a parent reading to or with a child an existing piece of literature that opens communication with the child about adoption issues. "Bibliotherapy is effective because you don't talk directly about adoption but metaphorically," he said. "It is a basis to probe feelings and trigger communication." It is usually most appropriate for children at an age when they are still being read to, usually age 12 or younger.

Therapeutic rituals can be effective for a child of any age if rituals are part of a family's life. A ritual could involve candle lighting, or planting and cultivating a memorial garden. A ritual can focus on grief or letting go of birth parents, or it can focus on the child's tie to her adoptive family.

Dr. Brodzinsky said that he had no disclosures. ■