Emergent and Worsening Suicide Ideation in Trials of Pediatric Paroxetine for Depression

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In September, 2004, the Advisory Committee of the U.S. Food and Drug Administration (FDA) recommended “black-box” warnings for antidepressants after finding a 2.15 overall risk ratio with users of paroxetine (Paxil®, GlaxoSmithKline), compared with non-users, in trials of major depressive disorder and an increased risk in aggregated data from clinical trials overall across antidepressants for suicidal behavior and/or ideation. The FDA evaluation focused primarily on the incidence of adverse drug events (ADEs) considered by blinded experts to be related to suicidality. A new analysis of depression studies with paroxetine by the manufacturer's researchers did not support that finding.

Dr. Fong examined suicide items from rating scales in three randomized, double-blind, placebo-controlled pediatric depression trials of paroxetine to observe worsening ideation and emergent ideation on the Hamilton Rating Scale for Depression (HAM–D), the Children’s Depression Rating Scale–Revised (CDRS–R), and the Montgomery–Asberg Depression Rating Scale (MADRS). The trials included 378 children and adolescents (7–18 years of age) who received from 10 to 40 mg/day of paroxetine or placebo.

“Emergent ideation” was defined by the appearance of specific items in patients without baseline ideation. “Worsening suicide ideation” was defined as an increase above the cutoffs for specific items at any point in the controlled phase of the trial.

An analysis of emergent suicide ideation in the three depression studies found no statistically significant differences within each study or overall in the combined data set (23.7% for paroxetine vs. 23.3% for placebo; \( P = 1.00 \)). The analysis of worsening suicidal ideation revealed a similar lack of difference between paroxetine and placebo, with a 15% incidence for paroxetine and a 14.3% incidence for placebo (\( P = .824 \)).

“In contrast to the signal from more suicidality adverse event reports on paroxetine in these clinical trials, suicide-item analyses failed to reveal a risk difference between paroxetine and placebo,” Dr. Fong concluded. “These results highlight the importance of understanding how rating scale assessments of suicidality may be discordant from actual adverse event reports.”

When asked to clarify the difference between the criteria used by the FDA's blinded experts and by Dr. Fong and to explain the absence of added suicide risk in the GlaxoSmithKline analysis, Mary Anne Rhyne, GlaxoSmithKline director of U.S. Media Relations, replied:

“GSK looked at rating scale items specifically related to suicidal ideation. The FDA’s analysis looked at spontaneously reported adverse experiences related to suicidality (suicidal ideation and/or attempt).”

Commenting on the tenor of presentations on suicide risk and antidepressants at this meeting, co-author Stan Krucewicz, MA, of GlaxoSmithKline, said:

“In talks this week, the physicians see a slight risk, which they monitor very carefully.”

Paroxetine is not approved for use by children or adolescents.

Efficacy of Escitalopram in Depressed Patients with Comorbid Anxiety

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A naturalistic study of escitalopram (Lexapro®, Forest) in depressed patients with concomitant morbid anxiety showed satisfactory control for symptoms of both conditions, according to a new study. The trial included both the high comorbidity rate for depression and anxiety and the need to see whether an agent already proven useful for each condition separately would be effective when both disorders were present. When a selective serotonin reuptake inhibitor (SSRI) has activating potential (i.e., insomnia is the most common side effect of escitalopram), the speaker said that the condition of patients who are anxious may deteriorate.

European comorbidity rates with major depression can vary between 10.2% for Social Anxiety Disorder and 33.7% for Generalized Anxiety Disorder. Among patients with depression, 50% to 70% have moderate anxiety and 20% to 25% have severe anxiety.

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anxiety. When both anxiety and depression are present, he
added, symptoms are more severe, impairment is greater, the
course is more chronic with a poorer outcome, the quality of
life is lower, the incidence of suicide is higher, and the uti-
lication of health care resources is increased.

To assess the efficacy of escitalopram in patients with major
depressive episodes with or without concomitant anxiety, the
investigators conducted a 12-week open-label, multicenter,
prospective naturalistic study in 217 French centers, mostly
community psychiatry clinics. Most patients started with
escitalopram 10 mg/day, with increases to a maximum of
20 mg/day.

The primary efficacy outcome measures were change from
baseline on the Hamilton Rating Scale for Anxiety (HAM–A),
and Global Clinical Improvement of Improvement (CGI–I) and
Patient Global Evaluation (PGE) scales. After the study, the
investigators stratified the 790 enrolled patients into three
HAM–A groups (210 with scores of 20 or below, 286 with
scores of 21–28, and 293 with scores of 29 or above). Sixty-one
percent of the enrolled patients (n = 478) had at least one
anxiety disorder.

HAM–A scores fell from 31.5 at the time of enrollment
in the study to 12.4 after 12 weeks. The responder rate (showing
a decrease of 50% or greater in HAM–A scores) was 72.1%. The
remission rate (defined as a HAM–A score of 12 or below) was
57.8%. HAM–A scores declined from 25.7 to 10.8 over the
study period.

Improvement in depression and anxiety scores was sig-
ificantly correlated (P < .001). However, Dr. Galinowski
pointed out that when either the severity of baseline anxiety
or the number of comorbid anxiety disorders was high, the
therapeutic effect on anxiety symptoms was increased but was
decreased slightly on depressive symptoms.

It was also noteworthy that the improvement in HAM–A
scores was not dependent on the presence of a coexisting
anxiety disorder. Approximately 71% and 68% of the subjects
were “responders,” defined as very much improved or much
improved on the CGI–I and PGE scales, respectively.

The withdrawal rate for treatment-emergent ADEs was 8%,
with nausea (12 patients out of 63) and headache (8 patients
out of 63) most common. Insomnia was reported in 3.9% of the
patients.

Dr. Galinowski said that although escitalopram is a more
potent inhibitor of serotonin reuptake than many SSRIs and
that some activating SSRIs can make patients very anxious,
escitalopram appears to be a potential solution “when other
SSRIs fail or when patients are anxious.” He did not have an
explanation as to why escitalopram’s potency was not ac-
companied by increased anxiety but did speculate that rela-
tionships between monoamines other than serotonin might be
involved.

**An Analysis of Two Medications for Attention-
Deficit/Hyperactivity Disorder**

**Author:** H. Lynn Starr, MD, McNeil Consumer & Specialty
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Two analyses from the Formal Observation of Concerta ver-
sus Strattera (FOCUS) trial—a comparison of osmotic
methylphenidate (OROS® MPH/Concerta®, McNeil) and
atomoxetine (Strattera®, Eli Lilly)—showed surprising symp-
tom improvement and responder rate benefits over time with
OROS® MPH in children with attention deficit/hyperactivity
disorder (ADHD).

The FOCUS trial examined the efficacy and tolerability of
both OROS® MPH, an extended-release, osmotic-delivery for-
mulation of methylphenidate, and atomoxetine, a selective
norepinephrine reuptake inhibitor (SNRI) developed as a non-
stimulant therapy for ADHD, stated Dr. Starr. She noted that
stimulant medications have long been recognized as a first-line
therapy for ADHD. They have demonstrated symptom
response rates as high as 70% to 90%. Clinical studies of atomox-
etine have shown efficacy comparable with that of immediate-
release methylphenidate.

The FOCUS trial enrolled 1,323 children (six to 12 years of
age) with newly diagnosed ADHD, according to the criteria
from the Diagnostic and Statistical Manual of Mental Disorders,
fourth edition (DSM-IV) and with symptoms that had been
inadequately managed by prior treatments.

The participants in this multicenter, randomized, prospec-
tive, three-week, open-label study were randomly assigned, in
a 2:1 ratio, to receive OROS® MPH (n = 850) or atomoxetine
(n = 473). OROS® MPH was initiated at 18 mg/day and titrated
upward at the physician’s discretion. Atomoxetine was initiated
at 0.5 mg/kg per day and was titrated similarly at the physi-
cian’s discretion. Assessment was performed via the ADHD
Rating Scale (ADHD–RS) and the CGI–Improvement (CGI–I)
scale. A parent/caregiver diary, the Parental Satisfaction Ques-
tionnaire (PSQ), was maintained as well.

The mean age of the children was 8.93 years, and 74% were
boys. The baseline ADHD–RS score was 39.3, and the baseline
CGI–S score was 4.69. Approximately 14% of children were
rated as inattentive, 12% as hyperactive/impulsive, and 78% as
combined. The mean dose after the first week was 32.7 mg
for the OROS® MPH participants and 36.7 mg for the atomoxetine
subjects.

At the end of the first week, the change in mean ADHD–RS
scores from baseline with OROS® MPH exceeded that of ato-
omoxetine by 2.8 points (P < .001). After the second week, that
difference grew to 3.5 points (P < .001). At week three, it grew
to 4.3 points (P < .001). The total change was approximately
20 points for OROS® MPH and 16 points for atomoxetine.

The percentage of responders (with a 40% or more reduc-
tion from baseline ADHD–RS score) was higher with OROS®
MPH than with atomoxetine at the first week (29% vs. 21%), at
the second week (48% vs. 37%), and at the third week (66% vs.
54%) (P < .0001).

The difference in CGI–I score responder rates (15.8% [68.6%
with OROS® MPH, 52.8% with atomoxetine]) was also signif-
icient in favor of OROS® MPH. The parental rating of treat-
ment effects favored OROS® MPH quickly and significantly
(P < .001), on the second day and at day 21, with strong
improvements observed in both groups.

The safety and tolerability of OROS® MPH and atomoxetine
were similar. Most ADEs were mild and consistent with prior
experience with the agents.

Dr. Starr concluded that although both agents achieved
significant symptom improvement, “OROS® MPH consis-
Meeting Highlights: APA

tently produced significantly greater improvement based on reduction in investigator-rated ADHD–RS scores."

The findings were similar for responder analysis, with CGI-I ratings of “much improved” or “very much improved” in parental assessments.

Dr. Starr pointed out that whereas ADHD occurs in both boys and girls, most of what is known about ADHD is derived from studies of boys. Furthermore, it is thought that ADHD in school-aged girls might often remain unrecognized and untreated because symptoms in girls may be less overt.

“They [girls] are not as big a behavior problem, so it is easy to miss them,” she said.

The inattentive ADHD subtype or combined type may be more prevalent than the hyperactive subtype. With a predominance of the inattentive subtype, girls tend to have greater cognitive and attentional impairment.

“We specifically wanted to see if these medications treat the inattentive as compared with the hyperactive subtypes,” she said in an interview.

Of 340 girls enrolled, 315 completed the study; 203 girls took OROS® MPH, and 112 took atomoxetine. Their response rates were similar to those of the boys. The OROS® MPH advantages over atomoxetine appeared for girls in all of the parameters measured for the overall group. A change was observed in the ADHD–RS (−20.2 vs. −16.5 points, \(P < .02\)), and improvements occurred in ADHD–RS inattentive subscale scores (−11 vs. −8.9 points, \(P < 0.05\)) and in the hyperactivity/impulsivity subscale (−9.2 vs. −7.6 points, \(P < 0.05\)). Response rates were higher with OROS® MPH (55.2%) than with atomoxetine (30.3%) (\(P < .01\)).

Treatment-related ADEs occurred in similar proportions (24.3% with OROS® MPH, 28.1% with atomoxetine), and the rate of ADE-related withdrawals from the study was similar (6.4% for OROS® MPH vs. 6.6% for atomoxetine).

Insomnia was more common in the subjects receiving OROS® MPH (6.9% vs. 0.8% with atomoxetine, \(P = .014\)), and nausea was more common with atomoxetine (8.3%) than with OROS® MPH (1.8%) (\(P = .008\)).

“We did not expect to see such an increasing difference in the symptom response rates, but that is what we found,” Dr. Starr stated. Girls in the OROS® MPH arm were 40% more likely to be responders.

With fewer overt symptoms in girls, how does one spot ADHD in them?

“It takes vigilant parents and teachers. When they are underperforming and not as focused as you’d like, you may have to raise the question,” Dr. Starr said.