Safety Issues in Child and Adolescent Psychopharmacology

In light of the continuing controversy concerning the use and safety of psychiatric medications in children and adolescents, several researchers in the field of child psychiatry met to discuss recent findings concerning adverse events in this population.

Assessing Safety Outcomes

Adverse event (AE) data in clinical trials of depression typically are collected using spontaneous reports that are given by patients in response to general questions (eg, "How have you been?" "What's been happening?"). Graham Emslie, MD, University of Texas Southwestern, Dallas, TX, discussed the prospective systematic approach that was used in the TORDIA (Treatment of Resistant Depression in Adolescents) and TADS (Treatment for Adolescents with Depression Study) trials.

Both trials used spontaneous reports; however, during the TADS trial, AE data also were collected using several self and clinician reports (one patient form, five clinician forms and one summary form). The TORDIA study added the Side Effects Form for Children and Adolescents (SEFCA), as well as a weekly clinician form for monitoring clinically significant worsening of symptoms. The investigators also conducted weekly consensus calls to discuss AE reporting and weekly calls to patients to monitor safety. Prodromal symptoms that were associated with an increase in suicidality were monitored, and all reports of suicide attempts were reviewed against a common definition.

In both studies, the investigators noted that different methods for eliciting AEs produced different results, which were at times associated with the background of the individual who was taking the report or were the result of unclear definitions. Dr. Emslie said, "More refinement is needed in the collection of adverse event data, including improved prospective measures and clarification and consensus among study sites on these AE definitions. Adequate training on all of these measures is critical."

Further reading: TADS [March J et al. *JAMA* 2004; Emslie et al. *J Am Acad Child Adolesc Psychiatry* 2006; https://trialweb.dcri.duke.edu/tads/index.html]. TORDIA [Brent et al. *JAMA* 2008].

Adverse Effects of Antipsychotic Treatment of Early Onset Schizophrenia Spectrum Disorders

Linmarie Sikich, MD, University of North Carolina, Chapel Hill, NC, presented unpublished data from the TEOSS (Treatment of Early Onset Schizophrenia Spectrum Disorders) study, a randomized, double-blind, 8-week trial that compared the safety and efficacy of once-daily doses of 3 antipsychotic treatments in youths aged 8-19 years with schizophrenia or schizoaffective disorder with active psychotic symptoms.

Safety was monitored at each visit using the following: systematically elicited adverse events, The Simpson Angus Extrapyramidal Scale, the Barnes Akathisia Scale, vital signs, skinfold thickness, and waist and hip circumference. Laboratory tests (CBC, SMA 20, leptin, insulin, C-peptide, HbA1c, free fatty acids, lipids, and prolactin) were conducted at Weeks 0, 4, 8, 24, 26, 52, or at termination. Patients also received an ECG and Abnormal Involuntary Movement Scale (AIMS) rating.

Highlights from the
American Psychiatric Association 2008 Annual Meeting

Approximately 50% of 116 subjects who received study medication withdrew before the end of 8 weeks because of lack of efficacy or side effects. Serious adverse events (SAEs) during the acute phase included 7 hospitalizations for worsening psychosis, which often was associated with suicidal ideation and aggression toward others. One hospitalization for severe urinary retention (risperidone) was reported.

Of the 54 subjects who entered the maintenance phase, 65% withdrew before the end of 12 months. One SAE occurred during the maintenance phase (hospitalization for dangerousness to others; risperidone). The primary reasons for withdrawal were lack of efficacy and side effects (primarily weight gain and akathisia).

A variety of AEs were seen during this study (Table 1). Some were significant and varied by medication and class. Dr. Sikich concluded, "We know that side effects differ among the antipsychotic medications, but we still don't know how to weigh them in terms of what keeps individuals on their medications and what the long-term health consequences are. There is remaining work to do."

Table 1. Adverse Events in Acute Phase.

	Molindone	Olanzapine	Risperidone
Any AE	36 (90%)	26 (74%)	35 (85%)
AE leading to treatment DC	8 (20%)	6 (17%)	5 (12%)
Weight gain	3 (8%)	17 (49%)	7 (17%)
Akathisia	17 (43%)	5 (14%)	4 (10%)
Increased appetite	3 (8%)	14 (40%)	7 (17%)
Constipation	1 (3%)	1 (3%)	7 (17%)
Sedation	16 (40%)	11 (31%)	13 (32%)
Irritability	9 (23%)	9 (26%)	8 (20%)
Agitation	7 (18%)	6 (17%)	5 (12%)
Anxiety	9 (23%)	3 (9%)	3 (7%)
Depression	4 (10%)	6 (17%)	5 (12%)
Insomnia	6 (15%)	2 (6%)	6 (15%)
Dystonia	1 (3%)	6 (17%)	5 (12%)
Blurred Vision	4 (10%)	0	4 (10%)
Irregular menses	2/17 (12%)	1/10 (10%)	2/14 (14%)

Stimulants and Risk of Vascular Events

The American Heart Association has suggested that children and adolescents receive an ECG before starting stimulants and that those who are already on stimulants receive one if they have not already done so [Vetter VL et al. *Circulation* 2008]. Mark Olfson, MD, Columbia University, New York, NY, reviewed some of the literature concerning possible relationships between stimulant use and cardiovascular disease.

Much of the concern over the risk of stimulant-associated cardiovascular effects comes from the adult literature, which shows some evidence that small increases in systolic blood pressure (BP) over a long period of time are associated with an increased risk for stroke [Prospective Studies Collaboration. *Lancet* 2002], as well as myocardial infarction and total mortality. A similar connection also has been seen with heart rate and cardiovascular mortality [Palatin P et al. *Arch Int Med* 1999]. The concern is that these small changes, when seen in youth over many years, may be associated with morbidity.

"While there are some data in youth that show statistically significant changes in diastolic BP and pulse over time [Findling RL et al. *J Am Acad Child Adolesc Psychiatry* 2001; Samuels JA et al. *Pediatr Nephrol* 2006], the question we need to ask as clinicians is, "Are these changes clinically significant?" said Dr. Olfson.

Winterstein and colleagues recently published results from a retrospective cohort study that followed youths aged 3 to 20 years who were newly diagnosed with ADHD. Stimulant use was tracked as: current, former, or nonuse (time preceding the first stimulant claim, including follow-up of youth who were never exposed to stimulants). Study endpoints were cardiac death, first hospital admission for cardiac causes, or first emergency department visit for cardiac causes. Results show that during 124,932 person-years of observation (n=55,383), there were 73 deaths (5 due to cardiac causes, none of which occurred during stimulant use). The incidence of cardiac events that required hospitalization was small and similar to national background rates (27 youths hospitalized; 8 current use, 11 former use, 8 nonuse). Stimulants were associated with an increase in cardiac emergency department visits (1091 youths). Former use did not confer an additional risk when compared with nonuse [Winterstein AG et al. *Pediatrics* 2007].

"We really don't yet have the kind of evidence that one would need before reaching a firm conclusion of a causal association between stimulants and risk of cardiovascular events in youth," said Dr. Olfson, noting that the current evidence is cause for caution, not alarm.