Report of the Therapeutic Working Group on Antipsychotic Drug Safety

19 November 2009

Bethesda, MD

Actions of Committee to Date

- We had 5 group conference call meetings
- We discussed the available data and shared questions regarding use, effectiveness and adverse events of atypical antipsychotic (AATP) drugs in children and adolescents.
- We arrived at a consensus re the following conclusions

Conclusions

- Atypical antipsychotic (AATP) drugs are widely used (Olfson, et al. 2006) in children and adolescents for a variety of indications, most of which are "off label"
- In addition, these drugs are often used in combination with other pharmaceuticals
- Findings from clinical trials (CTs) on the efficacy and safety of these drugs are often unrelated to community practice patterns

Conclusions (cont'd)

- Although CTs assess both efficacy and safety of atypical antipsychotics in children and adolescents, there are a number of limitations for assessing drug safety
- Limitations include: Relatively short term studies; small numbers of subjects; many exclusions and high drop out rates. Thus, CT data on efficacy and safety are limited in generalizability and lacking in long-term safety information

Conclusions (cont'd)

- Available data suggest there is efficacy for the currently approved indications but there are little published data to support the multitude of other uses currently seen
- Compared with adults, the incidence of adverse drug events is higher in many respects in children and adolescents. For example, increased lipid levels and weight gain

Findings from the available data

- Weight gain is a common ADR with AATP drug use, and may be extreme. Correll et al. (JAMA, October 2009): 4-19 year old mental health clinic patients had substantial drug-specific weight gain ranging from 4.4-8.5 kg/10.8 weeks
- Some of these patients develop other aspects of the metabolic syndrome, with potentially significant implications for future health

Findings from the available data

- Diabetes and diabetic ketoacidosis (DKA) may occur with use of these drugs. How often this occurs is not clear. Although most of the diabetes data are from studies in adults, notably there are a number of reported deaths in children with DKA. Of note, fatality is rare in other children with diabetes.
- Some subjects who become glucose intolerant or diabetic are not overweight raising questions about the prevalence of regular monitoring of AATP-treated youth for changes from baseline health status in relation to length of AATP exposure.

Knowledge Gaps - 1

A research focus is needed on reducing pediatric AATP knowledge gaps including

- Long-term safety
- Risk moderators, e.g. age group and gender
- Comparative safety data, e.g. Community vs. CT population
- New-users vs. prevalent users of antipsychotics
- Adverse Drug Effects risks in overweight youth
- ADE risks for AATP combinations with other rxs
- ADE risks in youth with serious comorbidities, e.g. chronic medical conditions in disabled youth

Knowledge Gaps - 2

- Inadequate utilization, efficacy or safety data on adjunctive AATP-therapy with drugs to control weight gain, e.g.
  - Metformin (Shin, et al. 2009)
  - Stimulant-AATP combination failed to attenuate weight gain in community-treated 7-17 year olds (Calarge, et al. 2009)

Knowledge Gaps - 3

- Longer term data on efficacy and adverse events
- Form longitudinal cohorts from retrospective data sources
- Large cohorts should have broad community-treated populations with various indications for use and across youth age groups

Knowledge Gaps - 4

- Studies examining interactions of atypical antipsychotic drugs with other drugs commonly used in combination, e.g. stimulants, SSRIs, anticonvulsant mood-stabilizers, etc.
- Studies to tease out determinants of efficacy and identify factors increasing the likelihood of significant ADEs (e.g., extreme weight gain, diabetes and hyperlipidemia)

Knowledge Gaps - 5

- Mechanisms of metabolic side effects of atypical antipsychotics: for example, identification of possible changes in neuro-endocrine systems (HPA axis or others) associated with weight gain and diabetes.
- Measures of known orexigenic (appetite stimulant) hormones and other systems associated with extreme weight gain. If changes in these measure are found, can they be used to predict problems?

Consensus regarding the current status

- Data are needed to illuminate both the effectiveness and safety for specific atypical antipsychotic drugs in children and adolescents
- Funding of studies to collect such data, including both retrospective and prospective long term studies should be a priority for the FDA and NIH

Consensus (cont'd)

Questions to be addressed include

- the absolute incidence and time course of ADEs
- the mechanisms of ADEs, particularly metabolic abnormalities
- the balance between ADEs and efficacy in specific groups (e.g., age, race/ethnicity, the poor and near-poor, disabled youth, etc.)

Pediatric Drug Safety Research Design Options

- Clinical question
  - What is the safety profile for antipsychotic (AATP) use in U.S. children and adolescents?
- Research question
  - What is the incidence of metabolic and extrapyramidal side effects abnormalities (outcomes, e.g. weight gain, liver function abnormalities, and hyperlipidemia) in relation to length of exposure (main independent variable) and conditional on observed practice patterns e.g., primary diagnosis & comorbidities; concomitant psychotropic medications and health status (chronic pediatric conditions; severity)

Available Data Sources

- FAERS spontaneous reports of ADEs (Woods, et al. 2002) showed increased pediatric reports for sedation, weight gain, liver function and tardive dyskinesia compared with adults
- Meta-analysis of clinical trial data
- Federal probability sampling surveys
  - NAMCS NHMCS; MEPS
- Administrative claims data from insured populations
  - Medicaid; Commercial: HMOs & Preferred Providers
  - Toward 'national' pediatric utilization profiles: e.g. asthma rx use in 86% of asthma-diagnosed youth among 4.26 million commercially-insured youth <18 year olds in 2004-2005 (Korelitz et al. 2008)

Limitations of AERS

- Passive surveillance
  - Underreporting (<10% all events, variable
  - Multiple reporting biases (e.g. publicity)
- Data
  - Quality of reports vary & they are often incomplete
  - Duplicates, missing age, confounding
- Analyses
  - Recognition of AE as a possible ‘signal’
  - Reporting rates are NOT incidence rates; lack denominator of use
  - Drug exposure data can only be projected

Source: MedWatch website

Potential Risk Study Designs

- Retrospective Models
  - Large claims-based: Cooper et al. (2009) launch FDA-AHRQ funded study to assess cardiac risks (mortality; MI; stroke) in 500,000 insured youth (Medicaid; Ca Kaiser; HMO Research Network and i3 Drug Safety) medicated with ADHD-medications. Following Winterstein, et al. 2008
  - More Controversial: Classic Case Control: Gould et al. (2009) found 1.4% frequency of stimulant exposure in pediatric sudden deaths compared with 0.4% in auto accident passenger deaths

Prospective Clinical Study Design Models

- CATIE study (2006) AATP effectiveness trial for adult schizophrenia trial independently conducted showing 2nd generation antipsychotics were more expensive without benefit of improved efficacy.
- Sikich, Findling et al. (2008) TEOSS NIMH-funded 8 week trial for early onset schizophrenia & schizoaffective disorders: No significant difference in symptom response to molindone (50%), olanzapine (34%), & risperidone (46%). Olanzapine and risperidone had significantly greater weight gain.
- Correll et al. (2009) JAMA report on weight gain in a systematic community-treated sample showing average olanzapine users weight gain of 8.5 Kg in 10.8 weeks

Proposal for A Mixed Model Design Approach

- Stage 1: Claims data analysis (approximately nationally representative) to estimate prevalence and incidence of AATP use to identify
  - the size of the AATP exposed population
  - the length of exposure: < 1; 1; 2;3;4 or 5 yrs.
  - Age, gender, race/ethnicity, diagnosis-specific, comorbidity and severity subgroups
  - the extent of the outcomes of interest

- Goal: to identify at-risk populations and generate hypotheses, e.g. how many adolescents 10-14 y/o with 3-5 year-AATP exposures?

Prospective Clinical Cohort Study

- Stage II: At experienced regional academic research sites (PPUs, RUPPs) enroll N youth to meet the targeted exposure criteria based on prior AATP-exposure
- A possible study protocol
  - Exclude patients with prior history related to the target outcomes
  - Written patient/parent consent
  - Assign to AATP monitoring protocol
  - Family survey on age of first AATP use; health history; self-reported adherence to treatment; adverse events; reasons for discontinuation
  - Follow patients quarterly for 2 years so that 3 prior year AATP-user now may have ≥ 5 years' total AATP exposure; 5 prior years' → ≥7 years' total AATP, etc. to establish long-term safety in community populations
  - Report incidence of adverse outcome(s) for the class of AATPs and for specific agents, if feasible
  - Stratify by length of exposure and cumulative mg exposure

Limitations and Strengths of a Mixed Model

- Limitations
  - Never been tried. Needs pilot to assess feasibility
  - Fear of lack of engagement, enrollment, and continuation must be addressed
  - Comparisons are tricky
  - Lumping and splitting questions
- Strengths
  - Committed to benefit/risk assessment in community-treated individuals
  - No good alternative if long-term safety is the issue

BPCA Antipsychotic Safety Therapeutic Working Group Recommendations

1. Funding is needed urgently to implement the Working Group's recommendations.
2. A deficit exists in needed data and studies for understanding pediatric antipsychotic therapeutics, particularly use over the long-term.
3. FDA should make short-term data available for secondary studies by investigators from the field.
4. The Working Group would like to recommend drafting a review article summarizing current knowledge and recommended directions.

BPCA Antipsychotic Safety Therapeutic Working Group Recommendations (cont'd)

5. The Working Group, the National Institutes of Health (NIH), and the Food and Drug Administration (FDA) need to collaborate to identify the relevant variables to be included in electronic medical records.

6. The Working Group needs to learn more about the FDA Adverse Event Reporting System (AERS, so that recommendations can be developed regarding its use for monitoring pediatric antipsychotic therapeutics.

7. A design needs to be developed for studies of risk factors/predictors of adverse drug events (ADEs) and the effects of long-term use of antipsychotic medications.

8.Animal models need to be exploited to address issues of toxicity, particularly with long-term use.

9. The Working Group has an important purpose and would like to continue its activities.

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