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Consensus Report on Impulsive Aggression as a Symptom Across Diagnostic Categories in Child Psychiatry: Implications for Medication Studies

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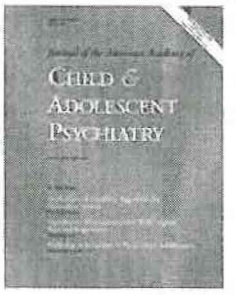

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Outline

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ABSTRACT

Objective: To determine whether impulsive aggression (IA) is a meaningful clinical construct and to ascertain whether it is sufficiently similar across diagnostic categories, such that parallel studies across disorders might constitute appropriate evidence for pursuing indications. If so, how should IA be assessed, pharmacological studies designed, and ethical issues addressed?

Method: Experts from key stakeholder communities, including academic clinicians, researchers, practicing clinicians, U.S. Food and Drug Administration, National Institute of Mental Health, industry sponsors, and patient and family advocates, met for a 2-day consensus conference on November 4 and 5, 2004. After evaluating summary presentations on current research evidence, participants were assigned to three workgroups, examined core issues,

and generated consensus guidelines in their areas. Workgroup recommendations were discussed by the whole group to reach consensus, and then further iterated and condensed into this report postconference by the authors.

Results: Conference participants agreed that IA is a substantial public health and clinical concern, constitutes a key therapeutic target across multiple disorders, and can be measured with sufficient precision that pharmacological studies are warranted. Additional areas of consensus concerned types of measures, optimal study designs, and ethical imperatives.

Conclusion: Derived from scientific evidence and clinical experience, these consensus-driven recommendations can guide the design of future studies.

In child and adolescent psychiatry the decision to initiate, change, or increase medication dose is often triggered by severe aggression in the child or adolescent who cannot be managed by caregivers. Patients with attention-deficit/hyperactivity disorder (ADHD)/disruptive behavior disorders, bipolar disorder, childhood psychosis, autism and other specific developmental disabilities, and internalizing disorders such as posttraumatic stress disorder (PTSD) and depression may present with aggressive behavior that is difficult for patients to contain and for caregivers to manage. Although there is an emerging literature on randomized, placebo-controlled trials in the treatment of a number of disorders in child and adolescent psychiatry and U.S. Food and Drug Administration (FDA) approval for some medications in the treatment of some of these disorders, the construct of impulsive aggression (IA) has not yet been fully agreed on or widely recognized as an appropriate therapeutic target. Nonetheless, evidence indicates that aggression often co-occurs in specific disorders, but may not be sufficiently ameliorated by standard medications used to treat these disorders (e.g., ADHD; see Aman et al., 2004; MTA Cooperative Group, 1999). Because there have been few rigorous clinical trials on the treatment of aggression in children with well-defined *DSM* disorders (other than conduct disorder), clinicians are often obliged to use "best guesses" for appropriate treatment strategies when IA complicates the management of ADHD, autism, bipolar disorder, PTSD, and other psychiatric disorders. Although treatment guidelines have been recently published concerning pharmacological management of aggression in the context of various *DSM*-defined conditions (Pappadopulos et al., 2003), it is notable that almost all of the recent controlled trial literature on which these guidelines were based was drawn from studies of children/youths who were required to meet criteria for conduct disorder (Schur et al., 2003). Pharmacological studies of autism have been the singular exception to this rule, and investigators have increasingly and successfully addressed IA and irritability as principal therapeutic targets in autistic patients (Research Units on Pediatric Psychopharmacology Autism Network, 2002).

A BRIEF REVIEW OF IA

Within appropriate contexts, aggression serves important survival and adaptation purposes. All human beings may express various forms of aggression on a frequent basis (from mild irritation to anger to verbal or physical aggression), but it can be maladaptive and constitutes one of the most common referral problems to child psychiatric clinics (Connor, 2002). Normal and maladaptive aggression overlap with, but are not identical to, delinquency (Connor, 2002, Steiner and Cauffman, 1998). Great care must be taken not to confound adaptive and maladaptive behavior for theoretical, empirical, and ethical reasons (AACAP, 1997).

Maladaptive aggression can be defined as aggression that occurs outside an expectable social context. The intensity, frequency, duration, or severity of the aggressive response is disproportionate to its causes and may occur in the absence of expectable antecedent social cues. The aggressive behavior is not terminated in an appropriate time frame and/or in response to feedback (Connor, 2002). Youngsters with maladaptive aggression have more school adjustment problems, greater deficits in cognition, and experience more peer rejection and victimization. They have difficulties in ambiguous interpersonal situations, such as reading emotion in people's facial expressions. In particular, they are far more likely to read a neutral expression as negative (disgust, fear, or anger), in contrast to normal youths who are more likely to read neutral faces as positive (surprised, happy, or kind; Best et al., 2002; McClure et al., 2003). In summary, maladaptive aggression can be reasonably well characterized as a symptom and can be differentiated from the willful or planned violation of societal norms, a form of aggression that serves an adaptive purpose (at least from the perspective of the perpetrator).

Basic neuroscience, epidemiological, and clinical studies provide considerable support for the existence of two subtypes of aggression. IA is unplanned and overt. The aggressor perceives the outcome of the aggressive act to be negative with negative accompanying emotions, such as frustration, regret, guilt, and fear (Donovan et al., 2003). Although planned aggression may result in the outward expression of a keenly felt negative emotion, such as disgust or contempt, unlike IA it is often covert, with the perpetrator anticipating a positive outcome, such as heightened interest, satisfaction, or happiness (Steiner et al., 2003). Factor and other analyses support these two constructs as overlapping (Malone et al., 1994) but relatively independent in school (Poulin and Boivin, 2000; Steiner et al., 2005a), clinical (Connor et al., 2004), and delinquent (Steiner et al., 2005b) populations, with IA more characteristic of clinical samples and covert or planned aggression more characteristic of delinquent or criminal populations.

Epidemiological evidence also supports this dichotomy. Developmental trajectories show antecedents predicting problems with IA from late preschool age forward, starting at about 4.5 years (Dodge, 1991; Dodge et al., 1997; Vitaro et al., 2002), including poor peer relationships and inadequate problem-solving patterns. Studies suggest that 21% of children with IA have a history of physical abuse (Dodge, 1991). IA is stable over time across the school years and becomes increasingly associated with diverse and significant psychopathology. In contrast, planned aggression starts at about 6.5 years and is associated with aggressive role models in the family rather than physical abuse (see Dodge, 1991; Dodge et al., 1997; Porter, 1998). Children with planned aggression attribute positive valence to aggression (Dodge et al., 1997).

Animal studies show that impulsive and proactive forms of aggression are associated with different patterns of brain activation (Blair, 2004). Rodent models of aggression suggest that there may be different neurobiological mechanisms associated with different models of aggression, even though some medications may be equally effective in damping down aggression, whatever the mechanism (Ferris and DeVries, 1997). Although there is mounting evidence that IA is a clinically distinct and important construct, associated with a wide range of psychopathology (Aman et al., 2004; Research Units on Pediatric Psychopharmacology Autism Network, 2002), to date it has not been clear that aggression is the same symptom across disorders in child psychiatry. Within specific disorders it has not been clear that the symptom of IA is discrete/separable in terms of treatment response from other symptoms of the disorder, nor has it been clear whether IA constitutes an appropriate and specific treatment target.

In spite of a lack of data from controlled clinical trials of IA as a distinct treatment indication, the preponderance of children and adolescents hospitalized in a large state inpatient system receive pharmacotherapy for the treatment of aggressive symptoms, with 40% receiving two or more medications, most commonly an atypical antipsychotic (Pappadopulos et al., 2002). Similarly, recent data from a representative national sample revealed that 18% of all child/adolescent visits to psychiatrists in 2002 included the use of an atypical agent, with the largest proportion of these visits for patients with disruptive behavior disorders and aggression (Olfson et al., 2006). Atypical agents appear to be most common, however, other agents used in the treatment of aggression in children and adolescents include anticonvulsants, stimulants, selective serotonin reuptake inhibitors, anxiolytics, [alpha]-agonists, [beta]-blockers, and sedatives (Connor, 2002; Steiner et al., 2003). Going forward, carefully executed clinical trials testing the role of these agents for IA management are critically needed to enhance the quality of clinical practice, to spare children from ineffective medications with accompanying side effects, and, ultimately, to improve overall outcomes.

Studies of aggression in children raise important ethical questions. Demographic and cross-cultural issues must be responsibly considered, so that study design, data, and conclusions cannot be used to impugn any group. Likewise, the role of well-established behavioral or milieu interventions that have been previously shown to be efficacious in aggressive children (Kazdin et al., 1989, 1992; Kellam et al., 1998; Lochman and Curry, 1986; Lochman and Lampron, 1988; Malone et al., 1997) must be considered, potentially as a precondition for or concomitant of pharmacological treatment.

METHOD

To define the field's state of readiness to initiate programs of research on IA treatment in children and adolescents with major psychiatric disorders, 40 experts in the field met at a 2-day consensus conference November 4 to 5, 2004, at which careful reviews of the literature and reanalyses of extant data sets were presented on each of the topics listed in Table 1.

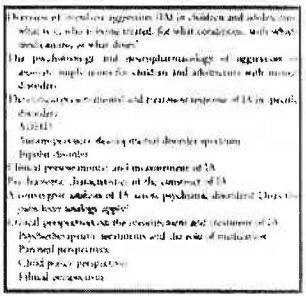

TABLE 1 Presentation Topics

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Participants

Conference attendees included leading clinical investigators in child and adolescent psychiatry, clinical scientists from major pharmaceutical companies with antipsychotic and anxiolytic drug products (or products under development), and leaders from government agencies (e.g., FDA, National Institute of Mental Health). Invitees also included parents and representatives from groups advocating on behalf of children and families, including the National Alliance for the Mentally Ill, Children and Adults With Attention-Deficit/Hyperactivity Disorder, and the Federation of Families for Children's Mental Health.

Meeting Format

During the first part of the conference, presentations laid out the state of scientific and clinical knowledge on the construct of IA, as well as the methodological and scientific challenges that need to be addressed. After the presentations, participants were divided into three workgroups and asked to address questions in each of three topic areas: assessment of IA, design of pharmacological studies, and ethical issues in pharmacological studies.

Assessment of IA.

* Is IA a sufficiently similar construct across diagnostic categories that parallel studies across disorders or studies with broad diagnostic inclusion criteria may constitute appropriate evidence to pursue an indication?
* How should IA be assessed? What, if any, current measures may be adequate for industry-sponsored studies of IA?
* Does intermittent explosive disorder (IED) "work" as a diagnostic category in youths, or would youths with significant clinical aggression be under- or overidentified? Although IED as a diagnostic category has rarely been used in studies of children, its usefulness in adult studies (Barratt et al., 1999; Best et al., 2002; Blair, 2004; Coccaro and Kavoussi, 1997; Coccaro et al., 1991, 2004; Kessler et al., 2006) may suggest the need to revisit the value of the greater use of this category in children and youths.
* What, if any, new assessment tools are needed? What studies should be done to validate these tools, and how should such studies be designed? How should such tools be studied across different age, ethnic, or gender groups?
* What other constructs should be assessed in IA and why?

Although conduct disorder has historically been associated with aggression, this diagnosis has been controversial and has been shown to be influenced by other factors, including hidden causal attributions held by diagnosticians when they become aware of additional environmental factors (Hsieh and Kirk, 2003; Wakefield et al., 2002). For these reasons, the conference objectives deliberately focused on disorders other than conduct disorder per se, although participants generally acknowledged and understood that many, perhaps most, children with IA may also meet criteria for conduct disorder. Somewhat less controversy has been attached to the design of treatment studies for other childhood mental disorders, such as depression, bipolar disorder, autism, and even ADHD, where the FDA has encouraged pharmacological studies and has approved indications for medications to treat these conditions in children and/or adults and where studies have suggested that the disorder may not simply be a function of environmental stressors (Rey et al., 2000).

Design of Pharmacological Studies.

* Should IA be studied across diagnoses, powered to test for the effect of diagnosis or within diagnosis (e.g., aggression within a disorder)? Which disorders would be most relevant and informative regarding the treatment of IA?
* Given multiple comorbidities in children and youths, how does one choose the primary disorder to be addressed? Should any disorders be excluded? Should

developmental disorders (e.g., IQ below 70 or 80) be studied separately?

* Should aggression be targeted only after treatment of the primary disorder has proven unsuccessful in sufficiently mitigating the impairment due to aggression? How vigorous should treatment of the primary condition have been to assume that it has failed? Should aggression treatment be an "add on" to whatever other medications or psychotherapeutic treatments the child is already receiving?
* Should IA be defined to have a certain duration (e.g., >6 months)? Should it occur in more than one setting (home only versus home and school versus school only)?
* Study population issues were addressed. How should age and gender be handled? Do any other demographic factors need to be considered separately? Should children in hospitals, residential settings, or foster care be targeted or disallowed?
* What should be the length of clinical trials, and how might that differ for different classes of agents? Should studies contain both acute and discontinuation phases?
* Are there particular agents or classes of agents that should be prioritized by "written request" from the FDA for future studies of IA?
* With regard to safety issues, how should behavioral (including cognitive) toxicity be addressed? Should a priori definitions for important behaviors such as activation and suicidality be used? For medications known to produce weight gain, should additional treatments, dietary management strategies, or other approaches be used to mitigate those problems?

Ethical Issues in Pharmacological Studies.

* Are any special ethical protections needed to ensure that children are not inappropriately placed in IA medication trials? What are these special considerations in terms of possible inclusion/exclusion criteria?
* Are special precautions or other preparatory steps needed before children are placed in such trials (e.g., psychotherapeutic or environmental interventions)?
* In terms of the risk-benefit balance, are there any populations at special risk of inappropriate inclusion in studies of IA, and, if so, what are they (e.g., youths in juvenile justice settings or under legal proceedings, ethnic minorities, or children in foster care)?
* Are placebo trials appropriate in youths with IA who have a preexisting condition such as ADHD/disruptive behavior disorders, autism, or bipolar disorder, or should trials only be "add-on" studies?
* Should any special considerations be taken to assess IA differently for various cultural or ethnic groups?

Because not all of the above questions could be addressed in the time available, each group determined its highest priority questions, focusing on those with the potential greatest importance for the field. Following the workgroups' deliberations, recommendations from each group were presented to the overall conference, and these recommendations were then further iterated to reach expert agreement about what is known, where there is consensus, and how the field should proceed with future pharmacological studies. These draft recommendations were then further refined after the meeting by all attendees, and the final recommendations with their accompanying rationale were developed, as detailed below.

RESULTS

Consensus Findings and Recommendations

Recommendations were reached in most but not all areas. Recommendations are ordered below in terms of their overall priority as established by conference participants rather than in the order of the original questions.

IA, as has been measured and studied to date, is in fact a sufficiently similar construct across diagnostic categories, such that parallel studies across disorders or broad diagnostic criteria can and should be conducted. Such studies, if appropriately designed, are interpretable and appropriate to pursue medication indications.

For this conference, a review of measurement instruments was conducted by researchers at Case Western Reserve University and Columbia University of recently published studies of aggression. After blind ratings of items by three expert raters (P.J., R.F., E.Y.), analyses indicated that the IA construct shows up on the Parent General Behavior Inventory, the Young Mania Rating Scale, the Aberrant Behavior Checklist, the Nisonger Child Behavior Rating Form, and the Child Behavior Checklist, with interrater agreement [kappa] values of.73 to 1.00 among raters. Of note, IA is actually a small subset of the items available on each of these scales (Fig. 1). IA items are largely found on the subscales for externalizing behavior, aggression, or delinquent behavior (across these scales). Analyses indicated that an IA factor with robust psychometric characteristics, good internal consistency, and high correlations among raters can be derived from these diverse scales. (Supporting data tables prepared by coauthor E.Y. are available on the *Journal*'s Web site www.jaacap.com via the Article Plus feature.)

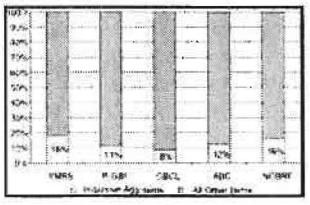

Fig. 1 Percentage of impulsive aggression items of total number of externalizing items by scale. YMRS = Young Mania Rating Scale; P-GBI = General Behavior Inventory (Parent Version); CBCL = Child Behavior Checklist; ABC = Aberrant Behavior Checklist; NCBRF = Nisonger Child Behavior Rating Form; *N* = 480.

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Compared to normals, receiver operating characteristic analyses completed on several separate studies and data sets available to the authors indicated that IA is significantly elevated in bipolar disorder, unipolar depression, and ADHD, but the symptom is not specific to any of these conditions and is less specific than the core symptoms of each disorder. Latent class analyses indicated that 50% to 90% of cases with any of the above Axis I diagnoses (allowing comorbidity with other psychiatric diagnoses) are accompanied by medium or high levels of impulsive aggressive behaviors versus less than 10% of youths without an Axis I diagnosis (Fig. 2). (Also see supporting data tables prepared by coauthor E.Y. via the Article Plus feature.)

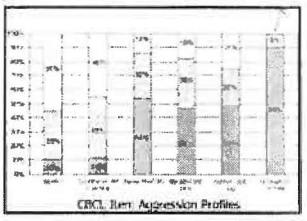

Fig. 2 Percentage of children meeting criteria for no, mild-moderate, or severe impulsive aggression construct. BP II = bipolar disorder II; BP NOS = bipolar disorder not otherwise specified; CBCL = Child Behavior Checklist; Disruptive Beh D/O = disruptive behavior disorders.

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Thus, IA is a construct that reflects a single latent variable that can be readily extracted from existing measures in empirically validated scales. It can be reliably recognized by expert raters and measured with high internal consistency. IA scores converge into a single factor across measures and raters. Although it is a sensitive marker of severity of psychopathology, with substantial elevations in clinical versus nonclinical groups, it is not a marker of a specific diagnosis, and it is less specific than the core symptoms of the *DSM*-defined conditions in which it is found. In effect, IA appears to be analogous to fever or pain because it can be reliably measured, is manifest across a variety of disorders, and is informative about the severity but not the type of illness.

Although the behavioral characteristics of IA can be captured by similar measurements across dissimilar patient groups, the likelihood of detecting a "signal" for an efficacious treatment is best achieved when clinical trials focus on the treatment of the symptom in patients with specific DSM-defined disorders. Therefore, given the current state of knowledge, for the purposes of pursuing pharmacological indications, IA should be studied principally within well-defined patient groups with well-established psychiatric disorders, such as ADHD, PTSD, autism, and/or bipolar disorder.

To the extent that other clinical conditions (e.g., pervasive developmental disorder [PDD], bipolar disorder not otherwise specified, personality disorders) can be well defined and operationalized, they also will warrant study, given the likelihood that IA characterizes these children as well. Each of these conditions poses unique challenges in study design. For example, although IQ restrictions for these studies are generally not needed, in studies of ADHD, it would make sense to undertake separate studies of youngsters with ADHD characterized by normal IQ and those with low IQ. Both groups would be worthy of study, even if one limits the heterogeneity of the sample for the purposes of a particular study.

Participants concluded that the IA construct can most fruitfully be studied within disorders such as ADHD, autism, PTSD, and bipolar disorder (i.e., those that are affectively overactivated and/or underregulated). Such studies should allow the determination of the extent to which IA accounts for overall clinical impairment, as well as the extent to which treatment benefits the primary disorder versus IA outcomes, illustrated at the conference and here below with three examples: ADHD, autism, and bipolar disorder. The rationale for studying IA within specific disorders is based on the fact that for psychiatric disorders, the FDA usually approves medication indications first within specific disorders rather for a symptom that cuts across multiple disorders. There are situations in which the FDA approves medications for symptoms not specific to any single disorder (e.g., fever, pain), even within psychiatry (e.g., agitation within dementia, suicidality within schizophrenia), but in most instances, the preferred approach is to first study a given medication's effects on a symptom in a single disorder. If it can be shown that the same agent is repeatedly effective on the target symptom across multiple conditions, then a more global indication may be sought.

ADHD: A sizable fraction of children with ADHD have significant problems with aggressive behavior. In the large (*N* = 579) multisite Multimodal Treatment Study of Children with ADHD (MTA Cooperative Group, 1999), four groups (optimal medication, optimal behavioral therapy, both combined, and usual community care) were compared. After 14 months of optimal medication treatment for children in the medication-only and combined treatment groups, 44% of 267 children with initial aggression remained significantly symptomatic. The continuing high levels of IA in this relatively unresponsive subgroup (constituting 26% of the total MTA sample) may have otherwise warranted some form of augmentation treatment, had the study design allowed for this option. (See supporting data tables prepared by coauthor P.J. via the Article Plus feature.) Although the MTA study design did not address the potential merits of additional pharmacological treatments, other research suggests that IA when comorbid with ADHD may respond to augmentation treatments, compared to placebo (Aman et al., 2004).

Of interest are the treatment recommendations for the use of atypical antipsychotic drugs in aggressive youths (TRAAY), a set of consensus recommendations adopted by New York State and Columbia University in partnership with leading investigators nationwide (Pappadopulos et al, 2003). Key aspects of the TRAAY algorithm are to treat the primary disorder with first-line treatments first (not aggression per se), to use monotherapy whenever possible, to use psychosocial and behavioral treatments for aggression, and, if/when all of these initial steps fail, to move on to concurrent use of an atypical antipsychotic drug to manage aggression.

Autism: In addition to the formal criteria for autism (onset before age 3, marked impairment in social interaction, restricted/repetitive patterns of behavior), *DSM-IV* indicates that other symptoms often become the target of treatment, such as aggressiveness, self-injurious behavior, severe temper tantrums, hyperactivity, and impulsivity. The class of drugs most studied for reducing these symptoms are the antipsychotics, in particular haloperidol (e.g., Campbell et al., 1978) and risperidone (Findling and McNamara, 2004; Snyder et al., 2002). Studies of these agents suggest that they both reduce symptoms associated with autism (including aggression), however, it is unclear whether early studies (haloperidol) and later studies (risperidone) are comparable, given substantial differences in study design, including patient selection and aggression assessment methods. Thus, in a recent study of children with autism (ages 5-17 years) who also met a criterion for disruptive behavior, risperidone treatment yielded substantial reductions in aggression compared with placebo (Research Units on Pediatric Psychopharmacology Autism Network, 2002). In contrast, in studies of children with autism (ages 2-7 years) not selected for aggression, the effect of haloperidol on aggressive symptoms appeared more variable (Anderson et al., 1984, 1989). An early meta-analysis of available studies of haloperidol did generally indicate some improvement in anger, uncooperativeness, and aggression, as well as hyperactivity and speech deviance in the drug group (Locascio et al., 1991).

Bipolar Disorder: Aggression is frequently reported in pediatric bipolar disorder. As part of the first phase of a multiphase prospective clinical trial, 139 youths ages 5 to 17 years with bipolar disorder were treated with combination lithium and divalproex sodium (Findling et al., 2003, 2005). Impulsive aggression was measured with the Young Mania Rating Scale (Young et al., 1978) and the Parent General Behavior Inventory (Youngstrom et al., 2001). Almost all of the participants showed some IA, but a substantial subgroup did not (Fig. 2). Although aggression explained only a small part of the variance in clinician-rated severity of manic symptoms, when compared with other symptoms of mania, aggression appeared to be less responsive to treatment and a key factor in mediating an inadequate therapeutic response in bipolar patients. Moreover, IA severity substantially predicted withdrawal from treatment in this study, again suggesting the importance of clearly separating impulsive aggressive symptoms from other symptoms of the primary disorder (see supporting data tables prepared by coauthor E.Y. via the Article

Plus feature).

The essential features of IA can and should be operationalized by clear clinical and research criteria, ascertained by careful clinical interview.

It is essential to define the inclusion and exclusion criteria and the clinical endpoints in clinical trials. Clearly naming, defining, and identifying the clinical entity (including distinguishing it from other clinical entities) is needed to gain FDA approval of a new drug claim for a symptom or disorder. IA assessments should characterize the history/nature/type of specific impulsive aggressive acts and their maladaptive nature, frequency, severity, duration, cross-situationality, triggers, contexts, consequences, presence of significant impairment, age of onset, and so forth. Such assessments must gather information about the child's aggression within already agreed-on and well-operationalized diagnostic categories (ADHD, bipolar, autism, PTSD), accompanied by careful specification of aggressive symptoms above a certain severity and/or impairment threshold. This information should be obtained by structured or semistructured interviews, both for ascertaining the specific nature of aggression and primary diagnoses. Such a semistructured interview is under development (modified from Barratt et al., 1999) and should define the nature, number, type, duration, and severity of specific impulsive aggressive acts in the context of the lack of major triggers, their cross-situationality contexts, and other factors (e.g., see Steiner, 2005a, b).

To develop appropriate participant groups for study entry, new assessment tools are desirable but not essential for new pharmacological studies to proceed in pursuit of a potential indication.

To determine the appropriateness of patients for referral to clinical trials in this therapeutic area, conference participants began with the assumption that most subjects would be referred from other treatment settings, generally because of the failure or limited effectiveness of treatments for conditions such as ADHD, bipolar disorder, or autism. Thus, it would be necessary to ensure that treatments for the Axis I *DSM-IV* disorder were adequate and that the investigators assess residual symptoms of IA before entering such children into the trial. Thus, claims for treatment indications of IA should be restricted to the disorder studied. By focusing on patients who have been carefully screened, evaluated, and determined to have persistent IA despite effective treatment of the core *DSM-IV* Axis I disorder, positive results of treatment of IA are less likely to raise a concern about pseudospecificity.

Age and gender also need to be considered because younger children (and boys) are more prone to irritability, temper tantrums, and other disruptive behaviors (Dodge, 1991; Dodge et al., 1997), and developmental differences should not be confused with non-normative, high levels of maladaptive IA in older patients. For example, a 4-year-old hitting another child must be considered differently from the same behavior in a 14-year-old. Likewise, punching a sibling may be considered differently from striking a teacher. Studies should be restricted to children older than 5 years, except in the instance of PDD or autism, in which children older than 3 years may be included. Conference participants agreed on the importance of assessing (and/or ruling out, depending on the study questions) the presence of psychosis, mental retardation, PDD, speech/language problems, nonverbal learning disabilities, substance abuse/dependence, lead intoxication, and severe traumatic brain injury because all of these factors have been found to be linked to increased aggression. The patient's IQ and family history, the history of any physical or psychological trauma or abuse, and an assessment of overall physical health should also be obtained. Finally, extending treatment studies to different cultural/ethnic groups raises concerns that aggression measures may not necessarily be interpreted in the same ways by each of the populations being studied. Such considerations require possible adaptation of questions that may be misinterpreted or misunderstood by diverse respondents. Field testing of measures, including the use of focus groups, should be considered to ensure item and questionnaire reliability and validity across cultural/ethnic groups.

Three types of assessments of IA symptoms may constitute a menu from which to select and to determine study entry: (1) trait measures, the underlying propensity to become physically or verbally aggressive with only minor provocations or frustrations; (2) characterizing/assessing recent impulsive aggressive acts; and (3) laboratory-based measures.

Currently available measures that tap the trait of IA include the Buss-Durkee Hostility Inventory (Buss and Durkee, 1957), the Life History of Aggression (Coccaro et al., 1997), the proactive versus reactive aggression scale extracted from the Achenbach instruments (Dodge and Coie, 1987), the State-Trait Anger Expression Inventory (Reyes et al., 2003), the Verbal Aggression and Provoked Physical Aggression subscales from the Children's Aggression Rating Scale (Halperin et al., 2002), and aggression subscales from the Child Behavior Checklist (Achenbach, 1991; Achenbach and Rescorla, 2001). Other assessments that may be useful include the Conduct Problem subscale from the Nisonger Child Behavior Rating Form, and the Irritability subscale from the Aberrant Behavior Checklist. Parents will usually be the primary reporter, although in some instances youth reports have proven useful (Nickel et al., 2005, 2006). However, if pervasiveness of aggression is important, then teacher informants will be required. Depending in part on the population and disorder studied, child self-reports also may be included.

Retrospective recall of information about the frequency or intensity of recent aggressive-impulsive acts or episodes may be one approach to characterizing/assessing recent impulsive aggressive episodes. Depending on the population and the aggression severity, the questionnaire or interview should ask respondents to recall episodes over the past 3 months, 4 weeks, 2 weeks, and past week. The Modified Overt Aggression Scale, which characterizes specific aggressive acts, and the Overt Aggression Scale-Modified of Coccaro et al. (1991, 1997) (see Malone et al., 2004 for use in children and adolescents) may be adapted for interviewing parents and children separately. Clearly, more development and study of possible IA measures in children and youths are needed.

Response inhibition, consequence sensitivity, startle response, and psychophysiological measures (e.g., autonomic responsivity) are useful laboratory-based measures that tap cognitive, emotional, and physiological domains relevant to aggression and/or impulsivity. By themselves, these measures are not sufficient to define inclusion criteria (or primary endpoints), but they may provide useful adjunctive information in proof of concept studies and may add some objective face validity to self-reports or parental reports. Laboratory measures, although expensive, may have merits in selected studies attempting to determine the impact of treatments on underlying brain processes and mechanisms of drug action.

Treatment response should be evaluated by a minimum of two complementary strategies: measurement of specific aggressive acts and measurement of aggressive/impulsive traits (and, in some studies, data from laboratory-based assessments of cognitive, emotional, and psychophysiologic functions associated with impulsivity or aggression).

Although each of the areas of assessment described in the previous section are also relevant to a consideration of treatment efficacy, a well-designed clinical trial requires the definition of a validated primary endpoint, as well as consideration of relevant and informative secondary endpoints. Conference participants recommended that at a minimum, these two complementary strategies must be evaluated to assess treatment responses (as primary and secondary endpoints), but the primary endpoint, in general, should be a change in the severity, frequency, and course of impulsive aggressive acts during treatment compared to baseline. Diary data should address counts, frequency, and severity of aggressive behaviors, whether the aggression is cross-situational, and the target of the aggressive act. Such data may be collected by diary or PDA and should be keyed to some scale, such as the Modified Overt Aggression Scale, to allow for data gathering efficiency

and concurrent validation.

IED may be a promising diagnostic category in youths, but there are few data available to support or require its use in lieu of the construct of IA.

IED is a categorical expression of IA and is more prevalent than previously thought, with 7% and 4% lifetime and 12-month prevalence rates, respectively (Coccaro et al., 2004; Kessler et al., 2006). Relatedly, in another study recently examining IED in a sample of 1,300 adult psychiatric outpatients, Coccaro et al. (2005) found that among with adult patients with IED (6.3% of the clinical sample), 30% had IED onset during their preteen years and about 75% had onset by the end of their teenage years. Although little research on IED in youths has been done to date, given the apparent usefulness of the construct in studies of adults with aggression, further studies of the applicability of the IED diagnostic category in youths are warranted. Such studies should focus on the question of IED comorbidity in children with other, currently accepted *DSM-IV* diagnoses such as bipolar, ADHD, PTSD, and autism/PDD.

Treatment trials should aim to detect a signal of the antiaggressive activity of drug X over some comparator (placebo or another drug).

A major issue in designing IA treatment trials in a cohort of patients with a specific *DSM-IV* Axis I disorder relates to the state of FDA-approved treatments for Axis I disorders in child and adolescent psychiatry. Although there are FDA-approved drugs for ADHD, it may be comorbid with disruptive disorders (e.g., oppositional defiant disorder, conduct disorder, conduct disorder not otherwise specified) for which there are no approved medications. No drugs have been approved for treating autism, and no drugs have yet demonstrated efficacy in registration trials for the treatment of bipolar disorder in children and adolescents. A previous consensus conference (Carlson et al., 2003) should serve as a guidepost in the design of studies of bipolar disorder in children and adolescents. Where drug treatments have been approved for the treatment of some other disorders (outside of child and adolescent psychiatry), the FDA has approved other drugs for specific aspects of these disorders that are not well addressed by standard therapies (e.g., agitation and suicidality in schizophrenia) and in other cases has endorsed development programs that target specific symptoms in certain disorders (e.g., psychosis in Alzheimer's disease, cognitive impairment in schizophrenia).

Thus, several design options are possible: (1) a two-arm add-on clinical trial design of patients with IA co-occurring with ADHD (and possibly also oppositional defiant disorder and/or conduct disorder), (2) a three- or four-arm comparison of monotherapy versus placebo and/or combination therapy in bipolar disorder, and (3) a two-arm monotherapy (versus placebo) study design in IA in autistic patients (Table 2 for various design and endpoint options recommended). Whether as an add-on therapy or as a monotherapy in patients with IA, study designs should be powered to provide documentation of the antiaggressive efficacy of the "serenic" (antiaggressive but not sedating) treatment.

TABLE 2 Recommended Designs for IA Clinical Trials

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The easiest situation to address is for a disorder that has standard treatments approved, but where these treatments do not adequately address IA as an aspect of that disorder (e.g., ADHD). An add-on design may be optimal for such situations. Another relatively straightforward design situation may concern a disorder that has no treatments for the primary disorder, but where IA is an aspect of the disorder that needs management (e.g., IA in autism). In such situations, testing a serenic versus placebo may be the most straightforward design option.

Other situations may not be so straightforward. For example, no drugs are yet specifically approved for pediatric bipolar disorder, although there are adult medications that may be expected to offer benefit in children. In this situation, it may be difficult to evaluate a trial testing a serenic versus placebo, with IA as the primary endpoint. A three-arm design may be a viable option, but studies involving comparisons between drugs often raise questions regarding fairness of the comparisons.

Given that IA tends to be chronic, the duration of FDA-approvable treatment studies were considered, with recommendations as follows:

* For initial efficacy: 6 weeks. Efficacy should be identifiable after 3 to 4 weeks of steady-state treatment (with studies lasting up to 6 weeks to detect a signal), but this will depend on the specific primary disorder and the particular agent. Previous controlled studies have established that efficacy may even be noted after 1 week, at least in studies of atypical agents (Schur et al., 2003).
* For long-term efficacy: 6 months of maintenance therapy. This length is not altogether arbitrary, given the fact that previous studies have shown that benefits may persist up to and even beyond this period of time Findling et al., 2004; Reyes et al., 2006; Schur et al., 2003).
* For safety: 1 year. Follow-up studies of side effects of treated aggression in children and youths have been conducted, appear feasible, and suggest that some initial side effects may dissipate over this period of time (Findling et al., 2004).

After efficacy/tolerability has been proven, long-term effectiveness should be further documented with a placebo-controlled discontinuation trial, after first stabilizing for >6 months of extended treatment, followed by randomly assigning subjects to placebo or continued therapy.

Special ethical considerations apply and must be addressed in clinical studies of IA in children and youths.

* Children in foster care or the juvenile justice system may be at special risk for inappropriate inclusion in studies of aggression. The possibility of such studies should not be excluded, however, because the most severely disturbed children with aggression are often found in these settings. At this juncture, priority should be given to studies limited to children with parents or legal guardians who can provide some history and informed consent and help monitor the children throughout the study. Nonetheless, children in the juvenile justice system have higher rates of IA, and studies of this population are clearly warranted when the necessary ethical protections are in place.
* In all studies, study developers must be cognizant of how the local community views aggression and whether patients, their families, and others in the community

from which subjects are drawn accept this as a disease or as a symptom necessitating a clinical intervention. In particular, studies including cultural/ethnic groups who have a history of being harmed by research participation and are distrustful of researchers would benefit from careful community consultation through all phases of the research process. Researchers should consider the use of mechanisms such as a community advisory board to ensure the integrity of this process. Because these studies are likely to involve multiple institutions and research sites, researchers and study sponsors should consider including such community consultation and advisory functions at the local, institutional, and coordinating center levels.

* The process of clinical trials must be made as transparent as possible without compromising the integrity of the research. It is important to make sure that parents, youths, and appropriate community representatives understand the study, its purposes, and its eventual possible outcomes and that information is communicated to them on an ongoing basis in understandable language. These are basic building blocks for trust and for ensuring that the study achieves its ultimate goals and is not misconstrued by others in the media or general public.

* Good information must be provided about potential adverse effects before, during, and after the trial has been completed, including new data collected in the trial. In the wake of the selective serotonin reuptake inhibitor black box warning for adolescents and the demand by leading journals that both positive and negative trials be reported, full disclosure of adverse effects is essential. If such data remain unpublished, pediatric prescribers may continue to prescribe off-label, unaware of specific side effects in children. Encouraging open disclosure and publication of all trials would keep the field more informed. In addition, trials should include systematic, prospective collection of adverse events information using state-of-the-art assessments to prevent the interpretation difficulties that can occur in post hoc analyses (e.g. selective serotonin reuptake inhibitor trials). The more carefully that such data are collected, the more valid any safety assessments and resultant patient-oriented information will be.

* Study designs must ensure that medical, mental, and environmental factors (biological, psychological, and social) that may be causing or contributing to the aggression are identified. When identified, if such factors may be otherwise effectively remediated, these steps should be attempted before study entry. Youths with IA caused by conditions that have been shown to be curable, treatable by other means, or attributable to specific causes other than the specific type of IA being studied should be excluded from medication studies until such factors have been satisfactorily addressed and the youths have been shown to have persistent high levels of maladaptive IA.

* Ethical considerations may warrant that where an approved treatment exists for a disorder (e.g., ADHD), add-on studies may be the preferred clinical trials design (i.e., testing the study medication versus placebo in children who are also being optimally treated for their preexisting *DSM* condition) rather than to deprive them of a medication or other treatment that is providing at least partial benefit. NIH-supported clinical research has demonstrated that a variety of environmental and psychosocial treatments can be effective for children with severe aggression. For example, multidimensional treatment foster care (MTFC) targets youths placed in group homes or training schools because of serious and chronic delinquency and/or aggression. Foster parents are contacted daily and supported continuously, and youths receive family therapy, skills training, individual treatment, and psychiatric consultation. Trials of MTFC versus group care have shown that measures of criminality and violence were markedly lower in MTFC versus group care youths (Chamberlain and Reid, 1998; Eddy et al., 2004). Although clinical trials examining the efficacy of MTFC in combination with specific pharmaceutical interventions have yet to be done, where demonstrated effective psychosocial interventions exist, medication studies should be considered for add-on study designs (e.g., with medication or medications added to a possibly efficacious psychotherapy intervention). Thus, trial designers may consider whether a standard program of anger management or behavioral therapy should be made available before, during, or throughout the efficacy trial. It may be during the midst of such trials (usually characterized by intensive monitoring and support, whether the participant is taking placebo or active drug) that new behavioral skills may be more easily learned and applied so that children and families have the necessary tools to cope more effectively after medication withdrawal and study cessation.

* "Safety nets" for children and families participating in such trials are essential. Because some children may show deterioration during a trial, exit rules and immediate access to a medical setting must be available if clinical worsening occurs to help ensure that the child is appropriately treated rather than ending up in the juvenile justice system. Parents have the same concerns in clinical trials as they do outside them: "Who's going to treat my child?" It is enormously challenging for families to deal with these youngsters, and they must have a clear path of options to pursue when problems arise.

DISCUSSION

The central finding of conference participants was that IA is in fact a sufficiently similar construct across diagnostic categories, such that studies across several disorders can and should be conducted. Such studies, if appropriately designed, are interpretable and appropriate to pursue medication indications. However, because the likelihood of detecting a signal for an efficacious treatment is best achieved when clinical trials focus on a single and distinct underlying *DSM*-defined disorder, given the current state of knowledge, IA should be studied principally within well-defined diagnostic groups, such as ADHD, autism, and bipolar disorder. It is understood that the safety/efficacy claim should not be extrapolated beyond the disorder that is studied to extend it to IA under all circumstances.

Although a gold standard for measuring IA does not exist and assessment methods are in need of further refinement, consensus was reached that current assessment instruments are adequate to conduct IA treatment studies. Additional studies of valid and reliable IA measures are urgently needed, however.

Clinical Implications

An increased appreciation of the differences between IA and proactive/planned aggression and the application of these distinctions in clinical, research, and medication development programs are likely to have a major impact on future treatment planning, public policy, and prevention programs. Clinicians and researchers alike should continue to explore and refine these distinctions to determine their full implications for our understanding of psychopathology, pathophysiology, treatment response, clinical course, and outcome.

Limitations

It should be noted that the final recommendations in this report were derived by a combination of data reanalyses, literature reviews, and expert consensus methods and are subject to human error or mistakes in interpretation. Thus, continued research of the merits of the constructs of IA and proactive/planned aggression is needed, as is an ongoing examination of the impact of these recommendations on future studies of aggression in children and youths.

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