ELSEVIER

European Neuropsychopharmacology 13 (2003) 305–311

EUROPEAN NEURO-PSYCHOPHARMACOLOGY

www.elsevier.com/locate/euroneuro

Conduct disorder: guidelines for investigating efficacy of pharmacological intervention☆

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Received 9 March 2003; accepted 10 March 2003

1. Introduction

In March 2001, the European College of Neuropsychopharmacology held a consensus meeting in Nice to address issues in the methodology for investigating pharmacological treatments for Conduct Disorder. These guidelines have been produced following the discussions.

2. Background

2.1. Features of conduct disorder

Conduct disorder refers to a clinical problem among children and adolescents that encompasses aggressive acts such as excessive levels of physical fighting, theft, vandalism, firesetting, running away, truancy, defying authority and other behaviours referred to as antisocial (Kazdin, 1995). These differ from the isolated, short-lived and relatively mild incidents that occur during normal development in being extreme, persistent and having important adverse consequences for the child and others. A related condition is oppositional defiant disorder, which lacks the overt aggression of conduct disorder but is marked by a pattern of negativistic, hostile and defiant behaviour expressed for example by verbal aggression, stubbornness, and deliberately annoying others. Oppositional defiant disorder is frequently the antecedent to conduct disorder (Loeber and Hay, 1997; Angold et al., 1999).

2.2. Epidemiology and burden of conduct disorder

The prevalence of conduct disorder is estimated at about 4% in 13–16 year olds, with boys more frequently affected than girls. There is an important comorbidity of conduct disorder and of oppositional defiant disorder with attention-deficit hyperactivity disorder (ADHD) (about 50% of the cases), depression (about 30%), anxiety disorders (30%), and learning disabilities (30–40%) (Angold et al., 1999).

The onset of conduct disorder may occur as early as age 5–6 years but is usual in late childhood or early adolescence. Oppositional defiant disorder often emerges gradually in the preschool years in the home setting, the full syndrome usually becoming apparent before age 8 years. These children mostly present with one or two symptoms of physical aggression, just failing the diagnostic threshold for conduct disorder that is set at three criteria, but many pass the threshold between the age of 8 and 14.

Conduct disorder, and oppositional defiant disorder, are stable diagnoses, particularly where onset is early, where there are a larger number and variety of symptoms, aggressive behaviours, comorbidity with ADHD, academic underachievement, and low intelligence.

Prognosis is relatively poor and conduct disorder is associated with later psychiatric disorder, antisocial personality disorder and substance abuse disorder. It is also associated with criminal behaviour, increased risk of marital breakups, early pregnancy, poor employment record, death related to violent behaviour. Between 30 and 50% of children with conduct disorder meet criteria for antisocial personality disorder in adulthood and virtually all adult cases of antisocial personality disorder are characterized by a childhood course of severe conduct disorder (Robins, 1978, 1991).

Twin and adoption studies provide evidence for a substantial genetic component in aggressive behavior and

☆ECNP Consensus Meeting, March 2001, Nice, France.

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0924-977X/03/$ – see front matter
doi:10.1016/S0924-977X(03)00046-4

there appear to be shared genetic factors between aggression and ADHD (Silberg et al., 1996) and aggression and temperamental problems (Gjone and Stevenson, 1997). Certain genes that control catecholamine metabolism such as tryptophan hydroxylase and monoamine oxidase seem to contribute to variation in aggressive behavior (Brunner et al., 1993). Individual risk factors for conduct disorder include ADHD, high impulsiveness, low intelligence, and weakness of executive functions of the brain. This is consistent with the finding that violent adults have decreased prefrontal cortical gray matter and glucose hypometabolism in the medial orbitofrontal region (Raine et al., 2000, 1997). Other neurobiologic correlates of aggressive behavior are decreased levels of brain serotonin (Coccaro et al., 1997), low autonomic activation as reflected in low resting heart rate and low skin conductance and weak mobilisation of endocrinologic stress responses (Van Goozen et al., 2000, 1998). Environmental factors that appear to be associated with an increased risk for conduct disorder and oppositional defiant disorder are poor parental supervision, harsh discipline, physical or sexual abuse, broken family, poverty and violent behavior of a parent (Lahey et al., 1999).

2.3. Current treatment

Currently there are no medications licensed for the treatment of conduct disorder in children and adolescents. In clinical practice in the USA conventional antipsychotic agents have been the most commonly prescribed drugs for children and adolescents with aggressive behaviour with a target symptom of aggression (Kaplan et al., 1994). Positive controlled trials in children with conduct disorder have been reported for haloperidol (Cunningham et al., 1968; Werry et al., 1975; Campbell et al., 1984; Greenhill et al., 1985), lithium (Campbell et al., 1984, 1995; Malone et al., 2000), methylphenidate (Klein et al., 1997) and risperidone (Findling et al., 2000; Buitelaar et al., 2001).

Most studies in conduct disorder have taken a symptom approach and have focused on aggression. We can anticipate that new compounds may modulate a broader spectrum of symptoms and studies are needed that cover the full range of conduct disorder and oppositional defiant disorder.

3. Diagnostic criteria

Controlled studies to establish efficacy of treatments for conduct disorder should use internationally recognized diagnostic criteria.

The definitions of conduct disorder and oppositional defiant disorder are generally similar in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) (Tables 1 and 2) and the International Classification of Diseases (ICD-10) (Tables 1 and 3) (World Health Organization, 1992; American Psychiatric Association, 1994). However, in ICD-10 there is an overall category of conduct disorder with oppositional defiant being a milder form, whereas in DSM-IV, conduct disorder and oppositional defiant disorder are separate disorders subsumed in the overall category of disruptive behaviour disorders. This conceptual difference remains a point of debate.

Table 1
Symptom domains for conduct disorder and oppositional disorder in DSM-IV and ICD-10

Oppositional disorder	Conduct disorder	
1. Tantrums	1. Lying	17. Stealing
2. Argues with adults	2. Initiates fights	18. Truant
3. Defiant	3. Uses weapons	19. Runaway
4. Annoying	4. Stays out late	20. Robbery/mugging
5. Blames others	5. Cruel to animals	21. Forces sex
6. Touchy	6. Cruel to people	22. Bullying
7. Angry/resentful	7. Destructive	23. Burglary
1. Spiteful/vindictive	8. Fire-setting	

In DSM-IV disruptive behaviour disorders also includes a residual category ‘disruptive behaviour disorder not otherwise specified’ for cases where impairment is clinically significant but there are insufficient symptoms of either disorder to meet the full diagnostic requirements. Conduct disorder requires the presence of, and impairment caused by three or more of the criteria, aggression to people and animals, destruction of property, deceitfulness or theft, serious violation of rules, during the past 12 months with at least one present during the past 6 months.

The ICD-10 describes an overall category of conduct disorders characterized by a repetitive and persistent pattern of behaviour in which, either the basic rights of others or major violations of age appropriate social expectations, that lasts for at least 6 months, and during which some of the symptoms listed in Table 1 are present.

For clinical trials the definitions used in DSM-IV are preferred as they are better operationalised. The definition of conduct disorder is, however, much more severe in DSM-IV than ICD-10. Most medication trials in conduct disorder have included subjects that were diagnosed according to the criteria of DSM-IV or its predecessors DSM-III-R and DSM-III.

4. Establishing a diagnosis

The diagnosis of conduct disorder and oppositional disorder is made almost exclusively on the basis of the history obtained from the parents or other family members, and teachers. Children older than about age 9 may themselves provide useful information about symptoms of conduct disorder and functional impairment.

A structured diagnostic schedule as part of the clinical assessment may be helpful. Currently available schedules

Table 2
Definition of conduct disorder and oppositional disorder in DSM-IV

Conduct disorder
A. A repetitive and persistent pattern is present in which the basic rights of others or age-appropriate societal norms or rules are violated, and three or more of the criteria 9–23 (Table 1) are present in the past 12 months and at least one criterion in the past 6 months.
B. The disturbance in behaviour causes clinically significant impairment in social, academic or occupational functioning.
C. If the individual is older than 18 years, criteria are not met for antisocial personality disorder.

Oppositional disorder
A. A pattern of negativistic, hostile and defiant behaviour lasting for at least 6 months, during which four or more of the criteria 1–8 (see Table 1) are present in a manner that is inappropriate for age and/or developmental level.
B. The disturbance in behaviour causes clinically significant impairment in social, academic or occupational functioning.
C. The behaviours do not occur exclusively during the course of a psychotic disorder or mood disorder.
D. The criteria are not met for conduct disorder, or (above age 18 years) for antisocial personality disorder.

include the Diagnostic Interview Schedule for Children (DISC-IV) (Shaffer et al., 2000) and Diagnostic Interview for Children and Adolescents (DICA) (Reich, 2000), which are respondent-based structured interview schedules that can be administered by lay interviewers and capture most psychiatric diagnoses that occur in children and adolescents using DSM-IV and ICD-10 criteria. The Schedule for Affective Disorders and Schizophrenia for School-age Children (K-SADS) (Kaufman et al., 1997; Ambrosini, 2000) and Child and Adolescent Psychiatric Assessment (CAPA) (Angold and Costello, 2000) are interviewer-based schedules that should be administered by trained clinicians.

It is recommended that a thorough clinical exploration be made by trained clinicians in conjunction with structured interviews in order to produce a diagnosis based on better information.

5. Patient sample

The population to be investigated in efficacy studies should be carefully defined. There is some evidence of a variation in conduct disorder according to age, for example the sex distribution varies. In order to address possible variations, data in both children (age 6–11 years) and adolescents (age 12–18 years) may be needed. Separate studies are indicated, or stratification of the study sample by age and separate analysis of the groups may be acceptable alternatives.

The results from studies of conduct disorder carried out in a mentally retarded population may not be fully generalisable to a normal population and additional studies will be needed.

Studies in conduct disorder meeting the DSM-IV criteria may be focused on the more severe end of the spectrum so that the results might not be generalisable to the oppositional defiant disorder population where the treatment will be used in those countries using the ICD-10 system. It is recommended that studies should be carried out in a population comprising both populations with the possibility of a subanalysis to determine possible differential effects.

Conduct disorder persists into adulthood but this is a controversial area for treatment studies. There is no established methodology and studies in this area will need to justify and validate the scales and methodology used. Studies in adults will need to exclude antisocial personality disorder, which is incompatible with the persistent diagnosis of conduct disorder.

6. Severity

In most psychiatric disorders it has proved difficult to establish efficacy when the illness is of mild severity. It is therefore important to include patients with a minimum

Table 3
Definition of subtypes of conduct disorder in ICD-10

Oppositional defiant type of conduct disorder
A. A type of conduct disorder usually occurring in younger children, primarily characterized by markedly defiant disobedient, disruptive behavior that does not include delinquent acts or the more extreme forms of aggressive or disssocial behavior
B. Four or more symptoms 1–23 (see Table 1) must be present but not more than two symptoms 9–23
C. The symptoms are maldaptive and inconsistent with developmental level
D. At least four symptoms have been present for at least 6 months

Conduct type of conduct disorder
A. A type of conduct disorder characterized by a repetitive and persistent pattern of behaviour in which the basic rights of others or major age-appropriate societal norms or rules are violated
B. Three or more symptoms 9–23 (see Table 1) must be present in the past 12 months and at least one symptom in the past 6 months

severity in efficacy studies and a minimum severity criterion is useful. The minimum severity criterion should be compatible with at least moderate severity.

There are few data on which to base a firm recommendation of a minimum score on a particular disorder specific scale for either conduct disorder or oppositional defiant disorder. A weekly minimum of three aggressive acts plus a minimum score of at least 18 on the Overt Aggression Scale (OAS) (Kay et al., 1988), and a teacher-rated minimum score of seven on the Iowa Aggression Scale, the defiant subscale of the Conners questionnaire (Halperin et al., 1990) have both been used in studies to define a minimum severity entry criterion (Klein et al., 1997; Malone et al., 2000). Other possibilities may be the clinical cutoff on the aggressive and delinquent scales of the Child Behavior Checklist (CBCL) for which norms are available in most countries (Achenbach, 1991). A minimum Clinical Global Impression (CGI) severity score of 4 or more (moderate severity) might be appropriate. However, these examples focus on aggressive behaviour. Depending on the purpose of the study, scales used and the expected results, other cut-off points may be more appropriate. The choice should be justified in the protocol.

The minimum severity criterion for inclusion in the studies will need to be defended. The criterion should be linked to the severity of conduct disorder or oppositional defiant disorder rather than to any comorbid disorders. It may be helpful for efficacy studies to establish a stable baseline of sufficient severity since this will help to define the persistent aberrant behaviour defining the disorder.

7. Comorbidity

To ascribe direct efficacy of a treatment in the specific condition under investigation it is necessary to take account of confounding comorbidities. Conduct disorder and oppositional defiant disorder are very frequently diagnosed in the context of various comorbid psychiatric disorders. Where a potential agent for conduct disorder has established, or potential, efficacy for a comorbid disorder that disorder should be excluded in pivotal studies. It may be helpful to exclude current major depressive disorder, obsessive compulsive disorder, post traumatic disorder, substance abuse disorders, lifetime schizophrenia or bipolar disorder, in addition to the usual exclusions of physical illness, etc.

Subsyndromal symptoms associated with these disorders that are frequently comorbid should be kept to minimal levels and carefully recorded in order not to confound the interpretation of the results.

ADHD, which is a very frequent comorbid condition, presents a particular problem where the agent under investigation has efficacy in ADHD, or antagonizes the effect of the test agent. In this case data in Conduct Disorder without ADHD are needed, either from at least one study in Conduct Disorder without ADHD, or, since it is difficult to find many patients with CD and not ADHD, in a study with prospective stratification provided its size gives sufficient power for separate analysis.

8. Severity scales

A number of severity scales completed by parents and teachers have been used successfully to measure response to treatment, both in placebo-controlled studies and in open studies. These include the Overt Aggression Scale (OAS) (Malone et al., 2000), the Modified Overt Aggression Scale (MOAS) (Buitelaar et al., 2001), the Aberrant Behaviour Checklist (ABC) (Aman and Singh, 1985), the Iowa Aggression Scale from the Conners questionnaire, and a conduct subscale of the Quay Revised Behavior Problem Checklist (Klein et al., 1997).

The Aberrant Behaviour Checklist (ABC) (Aman and Singh, 1985) has been widely used and has been found capable of distinguishing active treatment from placebo, even in the developmentally disabled (Buitelaar et al., 2001).

The Nisonger Child Behaviour Rating Forms (NCBRF) (Tasse et al., 1996) has been used successfully in placebo-controlled studies in both children and adolescents in developmentally disabled subjects (Aman et al., 2002; Snyder et al., 2002) and has been found to correlate well with the ABC.

Global scales such as the CGI-severity and CGI-improvement scales completed by the investigator have also proved to be effective in distinguishing treatments from placebo and been used in efficacy studies (Buitelaar et al., 2001; Aman et al., 2002; Snyder et al., 2002).

Other supportive criteria may be useful such as the need for additional therapy, and functional measures such as participation in social activities, school performance, family functioning, etc.

There are insufficient data to be sure of any one scale across all populations so that definitive recommendations are not possible at this time. More data are also needed on who would be the best rater (parent, teacher, psychiatrist) for clinical trials. The severity scales used to measure the severity of Conduct Disorder and oppositional defiant disorder in efficacy studies need to be internationally recognized, cover the core symptoms, and be validated, and be sensitive to change with treatment. The choice of the pivotal scale for assessing efficacy should be identified a priori. CGI will be useful as a supportive measure.

9. Choice of control treatment

Scientifically the most rigorous evidence of efficacy is obtained from randomized double-blind placebo-controlled group comparison studies. Such studies are feasible, have

been carried out, and have provided evidence of efficacy of a range of treatments, although as yet no licenses have been issued. Under such circumstances it is not possible to recommend the use of any comparator treatment to validate the study design or the assay sensitivity of the study population.

The usual requirement of positive results from a minimum of two well-conducted placebo-controlled studies to establish efficacy would seem to be appropriate in conduct disorder (including oppositional defiant disorder) provided that the analysis comprises the intention to treat (ITT) populations and dropouts are taken into account appropriately.

In Europe evidence of the persistent efficacy of treatment over a longer period is also required. Since there are limited data in this area it is difficult to make recommendations, although the duration of such studies will not be expected to exceed 6 months, in line with recommendations in other therapeutic areas. Studies establishing long-term efficacy provide more rigorous data when they are placebo-controlled.

10. Clinically relevant effects

A significant difference between a treatment and placebo may not necessarily register a clinically relevant change, particularly in very large studies. It is helpful to determine that the change seen on the scales is also clinically relevant. Since up to now no treatment is licensed it is difficult to be sure what response may be judged clinically relevant in conduct disorder or oppositional defiant disorder in the context of placebo-controlled studies

In the case of conduct disorder the behavioural instruments used to measure severity are themselves mostly clinically relevant. A significant change in these behaviours compared to placebo in moderately sized studies is likely to indicate a clinically relevant change.

It is helpful to determine whether the responder analysis is able to show a significant change compared with placebo since this has been taken in other therapeutic domains to indicate a clinically relevant change. If the responder definition is based on the clinician's global judgment, as with the CGI scales, this adds weight to the indication of a clinically relevant change. A definition based on the CGI change score of 1 or 2 (much or very much improved) has been used as has a definition based on the CGI severity scale.

In other therapeutic areas in psychiatry an arbitrary 50% improvement in symptoms on the pivotal scale is the commonly used criterion of responder and this has been used to define a clinically relevant change. Some studies in conduct disorder have used a mean global score of 2 on a 4 point scale to define a responder where the symptom or behaviour is only seen 'sometimes'.

Whatever criterion is adopted for a responder, it is more convincing if this criterion is identified in advance.

In long-term trials clinical relevance could also be supported by effects on social functioning and school behaviour and achievements but further research is needed in this area.

11. Dose

The recommended dose will need to be justified on the basis of the controlled studies in conduct disorder including oppositional defiant disorder. The optimal dose or dose range should be justified taking into account both efficacy and safety and might be dose-dependent. Appropriate pharmacokinetic studies in younger children and adolescents will form a basis for clinical studies. The most useful data for justifying the dose are derived from a multiple fixed dose study. The dose recommended will have to be justified as effective from the placebo-controlled studies.

12. Duration of short-term studies

The duration of the placebo-controlled studies should be long enough to allow the positive effects of the treatment to become evident but not so long that the dropouts on placebo or test agent confound the analysis. Experience with the existing positive placebo-controlled studies shows that efficacy is observed with various treatments at between 2 and 4 weeks depending on the size of the study and the particular problems with the design.

The recommendation is that a 4-week placebo-controlled trial period is justified but that a 6-week period is preferable. The choice of duration may, however, change if more comprehensive effects are being investigated.

13. Duration of long-term studies

The relapses reported on discontinuing treatment tend to occur rather rapidly and the relapse prevention design is therefore thought likely to establish that discontinuing treatment will increase the risk of a rapid return of the symptoms of the disorder. If this design is adopted a criterion of responder should be specified in advance to qualify to enter the randomization placebo-controlled phase of the study. In theory a responder criterion should reflect a low level of symptoms rather than a 50% reduction of symptoms, which might still leave substantial symptomatology and behavioural problems.

A deterioration of 25% has been suggested as a measure of relapse but the data to support this criterion are limited.

Other designs may be equally acceptable depending on the chosen endpoint.

No placebo-controlled data on the efficacy of long-term

treatment in conduct disorder are currently available. Clinical experience suggests that at least 6 months treatment is required and therefore it seems justified to require evidence of long-term efficacy of at least 6 months. In the absence of data precise recommendations on the length of studies are difficult.

14. Safety

All adverse events manifested at the time of the studies should be reported. The method of reporting of adverse effects, whether by means of spontaneous or elicited reports, questionnaires or other means, must be clearly stated and be appropriate for the age groups under study. Age appropriate normal laboratory values and clinical measurements should be utilized in adverse event reporting.

Medication may have effects on physical and cognitive growth and development, and the adverse event profile may differ in children and adolescents compared to adults. The particular issues of safety in children and adolescents need to be addressed. The dynamic process of growth and development may not manifest an adverse event acutely but at a later stage of growth and maturation. Preclinical safety data including appropriate neurobiological and behavioural studies relating to development, maturation, and growth in animals should be obtained prior to performing clinical trials in children. Long-term studies, either while patients are on maintenance treatment or during the post-treatment period, may be necessary to determine possible effects on skeletal, behavioral, cognitive, sexual and immune maturation and development.

Pharmacological studies will need to be undertaken to establish potential withdrawal dependence susceptibility. Specific analysis of clinical studies will be required in the EU to quantify the risk and duration of risk of the emergence of discontinuation symptoms.

15. Conclusion

Conduct disorder, whether defined by ICD10 to include oppositional defiant disorder or defined by DSMIV to exclude it, is a serious disorder which is sometimes dangerous. The disorder is one of the most frequent causes of referral of children and adolescents for specialist care and represents a very important public health concern. The long-term follow-up studies show that those with the disorder have an increased diagnosis of substance and alcohol abuse as well as other psychiatric disorders. In later life they suffer higher rates of marital breakup, poor employment record, a higher death rate largely associated with violence and greater levels of criminality. The disorder is therefore an appropriate target for treatment. Although many with the disorder are treated with a range of ad hoc treatments there is no treatment specifically indicated.

The guidelines here are derived from a considered assessment of the existing studies on conduct and oppositional defiant disorder and make suggestions about the design of studies which may help authorities to determine both efficacy and safety. Following these suggestions, we hope, may help allow new treatments to be developed and tested and allow a proper risk benefit assessment to be made.

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