Pharmacotherapy of Aggression in Children and Adolescents: Efficacy and Effect Size

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Abstract

Introduction: The treatment of pediatric aggression often involves psychotropic agents. Despite growing research on pediatric psychopharmacology, however, clinical issues regarding medication management of persistent behavioral problems remain poorly addressed. **Method:** A review of the literature from 1980 to November, 2005 yielded 45 randomized, placebo-controlled trials that addressed the treatment of aggression as either a primary or secondary outcome variable. Effect sizes (ES) (Cohen's *d*) were calculated for studies that met inclusion criteria. **Results:** Overall ES for psychotropic agents in treating aggression was 0.56. Despite variability in psychiatric diagnoses, select agents showed moderate to large effects on maladaptive aggression. Most studies focused on younger children (mean age = 10.4 years), and were of short duration (7 to 70 days). Largest effects were noted with methylphenidate for co-morbid aggression in ADHD (mean ES = 0.9, combined n = 844) and risperidone for persistent behavioral disturbances in youth with conduct disorder and sub-average IQ (mean ES = 0.9, combined n = 875). **Conclusion:** A growing literature supports the use of certain medications for managing pediatric aggression. Future studies should distinguish between impulsive and predatory aggression, and examine the efficacy of agents over longer treatment periods.

Key Words: aggression, pediatric psychopharmacology, effect size.

Résumé

Introduction: Les psychotropes sont fréquemment utilisés dans le traitement de l'agressivité chez les jeunes. En dépit des recherches de plus en plus nombreuses chez ce groupe d'âge, l'utilisation de la médication en clinique dans les troubles sévères du comportement demeure peu documentée. **Méthodologie:** Cet article consiste en une révision d'essais cliniques contrôlés et randomisés sur les effets de la médication psychiatrique sur l'agressivité auprès des populations pédiatriques. Nous avons également tenu compte de l'efficacité et de la taille de l'effet dans les études portant sur les catégories diagnostiques et les différentes classes de médicaments. De cette façon, les cliniciens obtiendront une meilleure compréhension de la pharmacothérapie de l'agressivité chez les jeunes. **Résultats:** Nous avons étudié 42 recherches contrôlées et randomisées, couvrant la période de 1980 à novembre 2005. En tout, la taille de l'effet a été de 0,72. Malgré la diversité des diagnostics, certains médicaments ont démontré des effets de modérés à importants sur l'agressivité. La plupart des études, généralement de courte durée (7 à 10 jours), traitaient des jeunes enfants (âge moyen de 10,4 ans). Les effets les plus importants se retrouvaient avec le méthylphénidate dans le traitement de l'agressivité chez ceux qui présentaient un déficit d'attention (taille moyenne de l'effet 0,9 un = 844) et la risperdone chez ceux présentant un trouble des conduites et une déficience intellectuelle (taille moyenne de l'effet 0,9, n = 875). **Conclusion:** Il existe de plus en plus d'articles au support de l'utilisation de certains médicaments dans le traitement de l'agressivité chez les jeunes. Des études ultérieures devraient tenter de différencier l'impulsivité de l'agressivité en même temps qu'examiner l'efficacité de ces molécules sur de plus longues périodes de temps.

Mots-clé: agressivité, psychopharmacologie, taille de l'effet

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Introduction

Maladaptive aggression, which is common in children and adolescents referred for psychiatric treatment (Bambauer and Connor, 2005; 2005; Kazdin, 1995), is a leading cause of pediatric psychotropic prescribing worldwide (Arehart-Treichel et al., 2004). In the current US diagnostic nosology, co-morbid aggression in youth is considered a nonspecific but serious symptom that is most often associated with attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD) (Connor, 2002; Findling et al., 2000;Jensen et al., in revision). It also co-occurs with autism (AUT) and the pervasive developmental disorders (PDD), mood disorders, post traumatic stress disorder (PTSD), and psychosis. Regardless of the primary psychiatric condition, chronic aggression is prognostic of longer and more intensive treatments, and poorer outcomes (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998; Werry, 1997). As such, it is a critical target for psychiatric intervention and research.

While studies show that various agents can effectively treat severe and persistent aggression in youth, the efficacy of medication treatments in real-world clinical settings remains unclear (Schur et al., 2003). In order to determine the degree of clinical change associated with an experimental treatment,

we can evaluate an *efficacious* treatment, or a treatment that renders a statistically significant benefit over a comparison condition (placebo) during a randomized controlled trial (RCT), in light of its *effect size* (ES), which allows for the comparison of change across studies.

Methods

Literature Search. The studies included in this review were identified in *Medline, PsychINFO,* and *EMBASE* searches of the literature from 1980 to November, 2005. We also examined the bibliographies of other published reviews for appropriate studies (most notably Connor et al., 2002a & b, Kutcher et al., 2004; Pappadopulos et al., 2004). Studies in this review met the following *inclusion criteria:* (1) employed a randomized controlled trial design with or without a drug free washout period, (2) explicitly addressed overt aggression, which describes physical or verbal confrontation with others, oppositional or defiant behavior, explosive outbursts or irritability, and the destruction of property, (3) reported the end point mean and standard deviation (SD) on a valid rating scale of overt aggression, CD, or ODD, or report significance testing and probability values, (4) were published in a peer reviewed journal, (5) studied children and adolescents < 19 years, with a mean age for the entire sample of > 6 years, and (6) were published in English. We conducted literature searches of pediatric psychotropic agents across medication classes (stimulants, SNRIs, antipsychotics, mood stabilizers, beta blockers, α-2 agonists and antidepressants) to identify published RCTs of children and adolescents with various conditions (anxiety disorders, mood disorders, pervasive developmental disorders, tic disorder, mental retardation (MR), etc.). Key search words, which included violence, assault, aggression, conduct problems, delinquency, antisocial behavior, overt aggression, and irritability were combined with the aforementioned searches. Four research associates conducted the literature searches and identified articles for possible inclusion in the review.

The studies presented here contain valid ratings of overt aggressive behavior even though the treatment of aggression may not have been a primary research question. Final decisions to include studies that did not clearly meet inclusion criteria were made by consensus of the authors. For a more detailed report of search terms and review procedures, please contact the corresponding author.

Forty-five studies met criteria for inclusion in this review. We eliminated several studies conducted prior to 1990 because they failed to report means or used invalid outcome measures. Also, several important studies employed head to head research designs and did not contain a placebo control group. These studies do not appear in the ES table but are discussed in the results section.

Calculation of effect sizes. ES values reported in Table 1 were calculated using Cohen's d (Cohen, 1988). ES were computed by finding the difference between the experimental and control groups on the outcome measure, and dividing this value by the pooled SD. As set forth by Cohen (1988), an ES less than 0.2 is considered a small effect; 0.21 to 0.5 is a medium effect; and greater than 0.8 is a large effect. Although ES is typically used to conduct a meta-analysis, it is increasingly recognized as an important tool that has been underused for interpreting the results of clinical trials (Weisz & Jensen, 1999). In medicine, effect sizes $\geq$ 0.4 are desirable because they are associated with observable changes in patients. While smaller effect sizes may be statistically significant, they often fail to predict clinically significant improvement.

Certain studies required ES calculations for multiple raters (clinicians, parents, and teachers). These values were subsequently averaged to determine the overall ES. Information regarding the ES values for each rater by study can be obtained by contacting the corresponding author. For studies that met inclusion criteria but did not report means or SDs, significance tests and probability values were used to calculate a Z score, which was then used to determine *d or* ES (Connor et al., 2002; Lipsey & Wilson, 2001; Rosenthal, 1991). All studies measured aggression at baseline and at study completion. Of the reviewed studies, 37 used a derivative of the Iowa Conners Rating Scale, 2 used the Overt Aggression Scale, 4 used the Aberrant Behavior Checklist, and 2 used the Nisonger CBRF. Several of these rating scales are reported to be highly correlated and appear to measure the same clinical construct (Aman et al., 1996; Hellings et al., 2005; Aman et al., 1985; Miller et al., 2004). The table also reports weighted means to account for the different sample sizes in each study.

Review of the Evidence on the Pharmacotherapy of Maladaptive Aggression in Children and Adolescents

Data regarding the use of psychotropic medications for the treatment of pediatric aggression is detailed in Table 1, which includes descriptive information about the study samples, primary and co-morbid diagnoses, medications tested, and the mean dose at study conclusion. All RCTs meeting inclusion criteria are organized by class and date of publication. Studies which compare medications from different classes are repeated in the relevant section and are marked with an asterisk (*). Like the table, the sections that follow are organized by medication class and review the existing literature on the efficacy of psychotropic agents across diagnoses. We also discuss issues pertaining to ES and pertinent clinical observations about the studies.

The most rigorous evidence on the pharmacotherapy of aggressive behavior in youth is comprised of 45 RCTs which report the effects of 52 independent medication trial comparisons (see Table 1). Of these, 18 were cross-over, 27 were a parallel design, and 19 employed a preliminary washout period. Subjects with a primary or co-morbid diagnosis of ADHD, ODD, or CD were included in 36 (80%) of the present studies. More than half of the studies required subjects to have a primary diagnosis of ADHD (51%, 23 studies) and 14 (31 %) allowed for a primary diagnosis of some combination of DBDs. The proportion of studies treating subjects characterized by other diagnostic categories was as follows: mental retardation/elective mutism/subaverage IQ (11%, 5 studies), autism or PDD (13%, 6 studies), and depression (2%, 1 study). Stimulants (40%, 18 studies) were the most studied class of medicine, followed by the atypical antipsychotics (20%, 9 studies), antidepressants (13%, 6 studies), mood stabilizers (13%, 6 studies), typical antipsychotics (7%, 3 studies), SNRIs (9%, 4 studies) and α-2 agonists (4%, 2 studies).

Stimulants

Stimulants are the most widely prescribed class of psychotropic agents for youth in the United States, Canada, and many other countries (Greenhill et al., 2002; Wolraich, 2003; Wong et al., 2004). Evidence from over 160 controlled trials of methylphenidate (MPH) (Ritalin), modified release MPH (Metadate CD), extended release MPH (Concerta), pemoline (Cylert), and amphetamine mixed salts (e.g. Adderall) has demonstrated the efficacy of stimulants in managing ADHD symptoms for up to 24 months (Abikoff et al., 2004; Greenhill et al., 2002; Weisz & Jensen, 1999). Despite their efficacy, however, stimulants can be associated with insomnia, reduced appetite, stomachache, headache, and dizziness. They have also been linked to long-term adverse events, including height and weight suppression (MTA Cooperative, 1999; Lisska & Rivkees, 2003). Since impulsive aggression often co-occurs with ADHD, ODD, and CD, data on the efficacy of stimulants for the reduction of impulsive aggression is derived from clinical trials that measure aggression as a secondary outcome variable.

We located 18 RCTs of stimulants (16 MPH, 1 combination of MPH and amphetamine mixed salts, and 1 combination of MPH, dextroamphetamine (Dexedrine), and pemoline that measured aggressive behavior. These studies examined a total of 1057 subjects (average n = 55.6; 84.2% male; age = 9.1 years). Primary diagnoses included in the studies were ADHD (13), AUT (2), MR (1), and DBD (3), and all but 6 allowed for comorbid diagnoses of CD, ODD, or ADHD. On average, study length was 27.2 days. The weighted average dose of MPH was 0.93 mg/kg/day. Higher methylphenidate doses were linked to stronger effect sizes.

Overall, stimulants exerted a medium to large effect (mean ES = 0.78) on pediatric aggression. This value, which is slightly lower than the ES (0.84) found in a previous meta-analysis of stimulant effects on overt aggression (Connor et al., 2002), may be due to the statistical influence of studies published after 2002 that met our inclusion criteria (see Table 1). MPH was notably effective with an ES of 0.9.

Selective Norepinephrine Reuptake Inhibitors (SNRI)

While stimulants are most frequently used to manage ADHD symptoms (Michelson, 2004), non-stimulant SNRIs, such as Atomoxetine (ATX) (Strattera), have been approved in the United States to treat children and adolescents who fail to respond or are intolerant to stimulants (Michelson, 2001). Although ATX is a relatively new medication and further studies are needed to explore its safety and efficacy in pediatric populations, research has indicated that it may be linked to decreased appetite and emotional lability (Kaplan, 2004).

We located 4 RCTs of ATX that measured aggressive behavior. These studies examined a total of 857 subjects (average n=214.3; 80.5% male; age = 10.5 years). The primary diagnosis for the subjects in each study was ADHD and

TABLE 1: Descriptive Characteristics & Effect Sizes of Studies

Study	Dx	Co Dx	Setting	Medication	Dose (mg/kg/d)	N	X Age	% Male	# Days	Effect size
STIMULANTS										
Pelham, 1985	ADHD	CD, ODD	OP	MPH	0.30	24	9.3	50	7	0.50
Pelham, 1987	ADHD	CD, ODD	OP	MPH	0.60	13	8.8	100	49	0.20
				MPH SR	0.60					0.40
Taylor, 1987	ADHD	CD	OP	MPH	0.74	37	8.5	100	21	0.50
Barkley, 1989	ADHD	-	OP	MPH	0.40	71	8.2	85	10	0.60
Pelham , 1989	ADHD	CD, ODD	OP	MPH	0.30	24	9.3	0	7	0.70
Gadow, 1990	ADHD	CD, ODD	OP	MPH	0.45	10	8.9	100	14	0.70
Aman, 1991*	subIQ, ADHD, CD	-	OP	MPH	0.40	30	10.0	83	21	0.90
Hinshaw, 1992	ADHD	CD, ODD	OP	MPH	0.38	44	9.5	100	35	0.95
Quintana, 1995	AUT	-	OP	MPH	0.79	10	8.5	60	28	0.50
Aman, 1997	MR	ADHD, CD, ODD	OP	MPH	0.40	30	7.7	73	14	0.30
Klein, 1997	CD	ADHD	OP	MPH	1.87	83	10.4	89	35	1.50
Bukstein, 1998	ADHD	-	OP	MPH	0.90	54	9.4	78	21	0.60
Smith, 1998	ADHD	CD, ODD	OP	MPH	1.18	46	13.8	89	35	0.80
Kolko, 1999	ADHD	CD, ODD	OP	MPH	1.35	16	9.6	100	42	0.50
Handen, 2000	AUT	ADHD	OP/IP	MPH	0.45	12	7.4	77	7	0.90
					0.90					1.10
Pliszka, 2000*	ADHD	-	OP	MPH	1.01	58	8.1	100	21	0.30
Wolraich, 2001	ADHD	-	OP	MPH OROS	1.10	282	9.0	83	28	1.10
MPH, WM					*0.93*	*50*	*9.3*	*83*	*25*	*0.86*
					Σ MPH =	844				
Pliszka, 2000*	ADHD	-	OP	AMS	0.50	58	8.1	100	21	0.60
Aman, 2004*	subIQ, DBD	ADHD	OP	MPH	1.10	155	8.7	83	42	0.52
				DEX	0.60					
				PEM	1.40					
STIM WM						56	9.1	84	27	0.78
					Σ STIM =	1057				
SNRI										
Michelson, 2001	ADHD	ODD, DEP, GAD	OP	ATX	0.50	296	11.2	71	56	0.25
Weiss, 2005	ADHD	ODD, GAD,	OP	ATX	1.20	150	9.9	80	49	0.15
Kaplan, 2004	ADHD	ODD	OP	ATX	2.00	89	10.0	80	63	0.13
Michelson, 2004	ADHD	ODD, DEP, GAD	OP	ATX	1.80	322	10.4	90	252	0.15
SNRI WM					**1.27**	**214**	**10.5**	**81**	**129**	**0.18**
					Σ SNRI =	857				
ATYPICAL ANTIPSYCHOTICS										
Findling, 2000	CD	-	OP	RISP	0.03	20	9.2	95	70	0.90
Buitelaar, 2001	ADHD	-	IP	RISP	0.04	118	13.9	100	42	0.90
Van Bellinghen, 2001	DBD	-	OP	RISP	0.05	13	10.8	39	28	1.96
Aman, 2002	subIQ, CD	ODD, ADHD	OP	RISP	0.04	118	8.4	82	42	0.70
RUPP, 2002	AUT	-	OP	RISP	0.07	101	8.8	81	56	1.10
Snyder, 2002	DBD	ADHD	OP	RISP	0.03	110	8.7	76	49	0.90
Aman, 2004*	subIQ, DBD	ADHD	OP	RISP	0.03	155	8.7	83	42	0.80
Shea, 2004	AUT, PDD	-	OP	RISP	0.04	77	7.4	77	51	1.20
LeBlanc, 2005	CD, ODD	ADHD	OP	RISP	0.04	163	8.4	72	42	0.80
ATYP (RISP) WM					**0.04**	**97**	**9.2**	**81**	**46**	**0.90**
					Σ ATYP =	875				

TABLE 1: Descriptive Characteristics & Effect Sizes of Studies

Study	Dx	Co Dx	Setting	Medication	Dose (mg/kg/d)	N	X Age	% Male	# Days	Effect size
TYPICAL ANTIPSYCHOTICS										
Campbell, 1984*	CD	-	IP	HAL	0.10	61	9.0	90	28	0.80
Anderson, 1989	AUT	-	IP	HAL	0.05	45	4.5	78	28	0.70
HAL, WM					*0.08*	*53*	*7.1*	*85*	*28*	*0.80*
					Σ HAL	106				
Aman, 1991*	Subav IQ, ADHD, CD	-	OP	THIO	1.75	30	10.0	83	21	0.35
TYP WM						**45**	**7.7**	**85**	**27**	**0.70**
					Σ TYP =	**136**				
MOOD STABILIZERS										
Campbell, 1984*	CD	-	IP	LITH	41.50	61	9.0	90	28	0.70
Carlson , 1992	CD	-	IP	LITH	28.00	11	8.5	100	56	0.80
Campbell , 1995	CD	-	IP	LITH	41.60	50	9.4	92	42	0.10
Rifkin, 1997	CD	-	IP	LITH	not reported	33	15.2	54	14	0.00
Malone , 2000	CD	-	IP	LITH	44.65	40	12.5	83	42	0.90
LITH WM					*34.40*	*38*	*10.8*	*84*	*34*	*0.50*
					Σ LITH =	195				
Cueva , 1996	CD	-	IP	CARB	23.55	22	9.0	87	42	0.00
MS WM						**36**	**10.7**	**84**	**38**	**0.40**
					Σ MS =	**217**				
α -2 AGONISTS										
Jaselskis , 1992	AUT	-	OP	CLON	0.01	8	8.1	100	42	1.10
Scahill , 2001	ADHD	Tics	OP	GUAN	0.07	34	10.4	91	56	0.40
α -2 A WM						**21**	**10.0**	**93**	**53**	**0.50**
					Σ α -2 A =	**42**				
ANTIDEPESSANTS										
Biederman , 1989	ADHD	-	OP	DMI	4.60	62	10.4	94	42	0.85
Black, 1994	MUT	-	OP	FLU	0.60	16	9.1	40	84	0.30
Emslie , 1997	DEP	-	OP	FLU	0.48	96	12.2	50	56	0.00
FLU, WM					*0.50*	*56*	*11.8*	*44*	*60*	*0.04*
					Σ FLU=	112				
Casat , 1987	ADHD	-	OP	BUP	6.00	30	9.0	83	42	0.55
Clay , 1988	ADHD	-	OP	BUP	5.30	33	9.3	96	28	0.00
Conners , 1996	ADHD	-	OP	BUP	4.50	37	8.5	92	28	0.30
BUP, WM					*5.20*	*33*	*8.9*	*91*	*32*	*0.30*
					Σ BUP=	100				
ANTID WM						**46**	**10.4**	**74**	**46**	**0.30**
					Σ ANTID=	**274**				
COMBINATION TREATMENT										
Aman, 2004*	SubIQ, DBD	ADHD	OP	RISP+STIM	0.04	155	8.7	83	42	0.80
					total Σ =	**3458**			**total ES**	**0.60**

Note: AMS = amphetamine mixed salts, ANTID = antidepressant, ATX = atomoxetine, AUT = autism, BUP = bupropion, CARB = carbamazepine, CLON = clonidine, DBD = Disruptive Behavior Disorder, DEP = depression, DEX = dextroamphetamine, DMI = desipramine, FLUO = fluoxetine, GAD = general anxiety disorder, GAUT = guanfacine, HAL = haloperidol, IP = inpatient, LITH = lithium, MUT = elective mutism, MPH = methylphenidate, MPH SR = methylphenidate (Sustained Release), OP = outpatient, PEM = pemoline, PDD = Pervasive Developmental Disorder, PIMO = pimozide, RIT = ritalin, STIM = stimulant nonotherwise specified, TICS = tics disorder, TS = Tourette's syndrome, WM= weighted mean, * = study repeated elsewhere in chart because it examines more than one medication.

secondary diagnoses included ODD, depression, and generalized anxiety disorder (GAD). On average, study length was 129.1 days. The weighted mean dose of ATX was 1.3 mg/kg/day. Overall, ATX exerted a small ES (mean ES=0.18) on pediatric aggression. ATX may not be an optimal psychotropic agent for treating pediatric aggression, given its modest ES over a relatively long average study duration and large average sample size.

Atypical Antipsychotics

Although atypical antipsychotics are first-line agents for schizophrenia and bipolar disorder in adults, they also show significant efficacy in the management of aggression (Schur et al., 2003; Sikich, et al., 2004). Atypicals are increasingly prescribed to children and adolescents for various psychiatric conditions (Pappadopulos et al., 2002; Patel et al., 2005). One study estimates that between 1997 and 2000, atypical use in pediatric populations increased from 2.4% to 5.1% (Martin & Leslie, 2003). Similarly, first time pediatric use of antipsychotic medications for subjects enrolled in TennCare doubled from 1996 to 2001 (Cooper, Hickson, Fuchs, Arbogast, & Ray, 2004). In another study, 25% of commercially insured youngsters (<19 years) prescribed an atypical were less than 9 years old and 80% male (Curtis et al., 2005).

Atypical antipsychotics have replaced conventional antipsychotics largely because of their decreased propensity for serious adverse events, such as neuroleptic malignant syndrome, extrapyramidal symptoms, and tardive dyskinesia (Connor et al., 2001; McConville & Sorter, 2004). Recently, however, accumulating evidence suggests that atypical antipsychotics are also associated with significant risks, including weight gain, type II diabetes, and cardiac rhythm abnormalities (Schur et al., 2003). In fact, the Food and Drug Administration (FDA) has required these agents to carry medical warnings regarding their tendency to induce profound weight gain and compromise metabolic functioning (Stigler et al., 2004; FDA, 2005).

Among first-line atypicals (risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), and aripiprazole (Abilify), risperidone is the most extensively studied medication for the treatment of aggression and CD in youth. Risperidone has been shown to produce significantly greater reductions in aggression and persistent behavioral disturbances compared with placebo in subjects with a variety of diagnoses, including CD (Aman et al., 2002; Findling et al.,

2000; Van Bellinghen & De Troch, 2001), autism (McCracken et al., 2002), ODD (LeBlanc et al., 2005), and ADHD (Aman et al., 2004; Buitelaar et al., 2001). Risperidone has also been effective for children and adolescents with subaverage intelligence (Buitelaar et al., 2001; McCracken et al., 2002; Snyder et al., 2002; Van Bellinghen & De Troch, 2001). In two large, parallel, multi-center trials (Aman et al., 2004; Snyder et al., 2002) of youth with persistent behavioral disturbances and subaverage intellectual functioning, risperidone treatment reduced socially dysfunctional, aggressive, and defiant behaviors, and caused mild to moderate extrapyramidal symptoms, somnolence, headache, weight gain, and prolactin elevations. Subjects (n=50) assigned to a follow-up study sustained these improvements over 48 weeks (Turgay et al., 2002). Similarly, in a study of 163 children with CD and ODD, risperidone-treated subjects experienced a decline in aggression that was approximately 2.6-fold greater than that experienced by members of the placebo group (LeBlanc et al., 2005). Although risperidone appears to be effective for the management of aggression, controlled trials of other atypical agents are rare (Schur et al., 2003). Given current side effect concerns and the rates at which atypicals are being prescribed to pediatric populations, future research should examine the safety and efficacy of other atypicals for co-morbid aggression.

We located 9 RCTs of atypical antipsychotics that measured aggressive behavior. These studies examined a total of 875 subjects (average n = 97.2; 81.1% male; age = 9.2 years). The studies included primary diagnoses of ADHD, CD, ODD, DBD, PDD, subaverage IQ, and AUT. Five studies allowed for comorbid diagnoses of ODD and ADHD. On average, study length was 45.7 days and the mean dose of risperidone was 0.04 mg/kg/day. Overall, atypical antipsychotics exerted a notably large ES (mean ES = 0.9), given the modest average dose of risperidone. ES generally increased with study duration.

Typical Antipsychotics

Compared with atypical antipsychotics, older typical agents are less frequently prescribed because they have been linked to a higher prevalence of extrapyramidal symptoms and dyskinesia in children and adolescents (Connor et al, 2001; McConville & Sorter, 2004). Recently, however, the CATIE study has contested the benefits of atypical agents, showing no significant differences in effectiveness or extrapyramidal symptoms between perphenazine (Trilafon), a

conventional drug, and second-generation atypical medications in adults with schizophrenia (Lieberman et al., 2005). The application of these findings to child populations is unclear but warrants further study.

Although early studies suggest that low doses of typical antipsychotics are effective for managing aggressive behaviors (Anderson et al., 1989; Campbell et al., 1982; Cunningham et al., 1968; Werry & Aman, 1975), others indicate that they can produce debilitating side effects and may not be optimal for the treatment of aggression. In one study of haloperidol and lithium carbonate for the treatment of youth with conduct disorder, optimal doses of haloperidol produced adverse effects that interfered with daily functioning more than those seen with lithium carbonate or placebo (Campbell et al., 1984). Another study of children with attention deficit disorder or CD showed that thioridazine (1.75 mg/kg/day) had relatively minor behavioral effects and was inferior to methylphenidate on teacher ratings of problem behavior and in the amount of absolute change produced (Aman, et al., 1991). Future research on the use of medium potency antipsychotics in children and adolescents is needed to determine the therapeutic potential of these agents for aggression.

We located 3 RCTs of typical antipsychotics (2 haloperidol (Haldol) and 1 thioridazine (Mellaril)) that measured aggressive behavior. These studies examined a total of 136 subjects (average n = 45.3; 84.5% male; age = 7.7 years). Primary diagnoses included in the studies were ADHD, CD, AUT, and subaverage IQ; no comorbid diagnoses were reported. On average, study length was 26.5 days. The mean dose of haloperidol was 0.08 mg/kg/day. Overall, typical antipsychotics exerted a medium ES (mean ES = 0.7). Both haloperidol studies, which were conducted on inpatient settings, demonstrated a large average ES (0.8) while thioridazine had a much smaller ES (0.35).

Mood Stabilizers

Research shows that mood stabilizers, which are commonly used for bipolar disorder, can also reduce aggressive symptoms associated with CD (Findling et al., 2000; Kafantaris et al., 1992; Malone et al., 2000). Four RCTs have shown that lithium (Eskalith, Lithobid) treatment can reduce bullying, fighting, and temper outbursts in severely aggressive, inpatient youth with CD (Campbell et al., 1984; Campbell et al., 1995; Carlson, et al., 1992; Malone et al., 2000). The use of lithium in children and adolescents, however, is often

deterred by the need for frequent blood draws for dose monitoring, as well as its associations with nausea, vomiting, enuresis, ataxia, fatigue, cognitive dulling, and weight gain (Bassarath, 2003; Malone et al., 2000).

Two studies that did not qualify for this review report that divalproex (Depakote), like lithium, can also reduce aggressive symptoms. In a seven-week cross-over RCT of 71 youth with CD, subjects receiving higher doses (500-1500mg/day) of divalproex experienced greater global improvement scores and self-reported impulse control than subjects randomized to low doses (250 mg/day) (Steiner, Saxena, & Chang, 2003). Similarly, in a study of youth with explosive temper and mood lability, divalproex treatment was superior to placebo in reducing aggressive symptoms (Donovan et al., 2000).

The use of carbamazepine (Tegretol) and other anticonvulsants has nearly doubled from 1994 to 2003 (Hunkeler et al., 2005). However, controlled trials of these agents are limited, and the one existing RCT of 22 inpatient youth with CD showed that carbamazepine was no different than placebo in reducing aggression and explosiveness (Cueva et al., 1996). Carbamazepine has been linked to serious adverse events, including hepatotoxic, hematologic, and metabolic concerns (Cummings & Miller, 2004). Since pilot and case studies indicate that carbamazepine can produce clinically and statistically significant declines in aggressiveness and explosiveness (Evans et al., 1987; Kafantaris et al., 1992), further research is warranted to fully establish its behavioral efficacy in pediatric patients.

We located 6 RCTs of mood stabilizers (5 lithium, 1 carbamazepine) that measured aggressive behavior. All studies were relatively short (mean length = 38.4 days), inpatient trials. These studies examined a total of 217 subjects (average n = 36.2; 83.8% male; age = 10.7 years) with a primary diagnosis of CD and no reported comorbid diagnoses. Doses of lithium fell between 28 and 44.65 mg/kg/day (average dose = 34.4 mg/kg/day). Blood serum levels of lithium were reported between 0.8 mEq/L and 1.12 mEq/L, within the published therapeutic levels (Perry et al., 1984).

While the mean effect size (0.4) for mood stabilizers was moderate, these studies demonstrated significant variability in the efficacy of lithium for comorbid aggression and corresponding ESs (range = 0.0 - 0.9). The lowest ES (0.0) occurred in a 2-week, parallel-group RCT of

lithium in 33 children with CD (Rifkin et al., 1997) which may have been too short to actualize any clinical benefits. The greatest ES (0.9) was produced in a double-blind, RCT of 40 inpatient youth with CD (Malone et al., 2000). This study is particularly important because it shows that lithium can produce measurable improvements in behavior within 42 days of inpatient treatment.

α-2 Agonists

Current research indicates that α-2 agonists can reduce oppositional behavior, enhance frustration tolerance, and improve hyperactivity and impulsivity in children with ADHD, CD, PDD, and Tourettes Disorder (Cohen et al., 1979; Cohen et al., 1980; Hunt et al., 1985; Jaselskis et al., 1992; Leckman et al., 1991). The efficacy of the a-2 agonist clonidine (Catapres) was supported in a meta-analysis of 11 double-blind RCTs, published from 1980 to 1999, which showed that clonidine exerts a moderate effect on symptoms of ADHD and may help to ameliorate impulsive aggression (Connor et al., 1999). An examination of Medicaid prescribing trends for youth across two US Mid-Atlantic States revealed that clonidine is often co-prescribed with stimulants (dosReis et al., 2005). In an RCT of 67 children (6-14 years) with ADHD and comorbid ODD or CD, a combination of clonidine and stimulant treatment improved conduct problems (Hazell & Stuart, 2003). Although clonidine can produce drowsiness and dizziness, it may also reduce the side effects associated with stimulant treatments.

We located 2 RCTs of α-2 agonists (1 clonidine, 1 guanfacine (Tenex)) that measured aggressive behavior. These studies examined a total of 42 subjects (average n = 21; 92.7% male; age = 10.0 years). Primary diagnoses included autism and ADHD; subjects with ADHD had comorbid tics. On average, study length was 53.3 days. The mean ES for these 2 trials adjusted for sample size was 0.5. Guanfacine produced a medium effect size (0.4) in an 8-week RCT of 34 children with ADHD and a tic disorder (Scahill et al., 2001), and clonidine produced a large effect (1.1) in eight male children with autism over a 6-week period (Jaselskis et al., 1992).

Antidepressants

The use of antidepressants for the management of aggression remains questionable. Although some data suggests that certain antidepressants, such as bupropion (Wellbutrin) and fluoxetine (Prozac), may have the potential to address aggression associated with depression, recent concerns regarding their safety in children and adolescents have discouraged their use. Evidence from clinical trials suggests a low but persistent link between Selective Serotonin Reuptake Inhibitor (SSRI) treatment and an increased risk for suicidal ideation and agitation (Cipriani, et al., 2005; Fergusson et al., 2005; Geller, et al, 1999; Whittington et al., 2004). The FDA has accordingly issued a "black box warning" that calls for increased physician and parental supervision of pediatric antidepressant use, particularly when medications are first prescribed, changed, or discontinued (FDA, 2005; Rosack, 2004a, 2005b). Although there are various studies testing the use of antidepressants for depression, few examine their effect on aggression.

We located 6 RCTs of antidepressants measuring aggressive behavior. One tested desipramine (Norpramin) (4.60 mg/kg/day), two studies tested fluoxetine (mean dose = 0.5 mg/kg/day), and three measured bupropion (mean dose = 5.2 mg/kg/day). These studies examined a total of 274 subjects (average n = 45.7; 74.2% male; age = 10.4 years). Primary diagnoses were ADHD (4), depression (1) and elective mutism (1). On average, study length was 45.8 days.

Overall, the average weighted ES for antidepressants was small (0.3) with significant variability across studies (range = 0.0 - 0.85). Desipramine produced the greatest impact on aggressive behavior in a 6-week RCT of 62 children and adolescents with ADHD (Biederman et al., 1989). Another study showed no therapeutic benefit of fluoxetine on aggression in 96 youth with depression (Emslie et al., 1997). The ESs of three studies on the anti-aggressive effects of bupropion in ADHD ranged from 0.0 to 0.55 in 100 youth.

Beta Blockers

Published reports on the use of beta blockers to treat aggression are limited. A literature review (Connor, 1993) that reported on the results of 31 studies of children and adults showed that beta blockers may lead to some tentative improvements in aggression, as did one open label trial of adjunctive nadolol (Corgard) (Connor et al., 1997). We could not locate any RCTs of beta blockers in youth.

Discussion

Although medication is commonly prescribed to address serious and persistent maladaptive aggression in youth (Pappadopulos et al., 2002; Patel et al., 2002), critical methodological challenges make research on aggression difficult to execute and interpret. Our limited understanding of the causes of aggression prevents its inclusion in the current US diagnostic framework. Co-morbid aggression is therefore often regarded as a nuisance, rather than a target of intervention in medication trials.

Current research considers aggression a physical behavior that generally causes harm or damage to objects or living beings (Volavka & Citrome, 1999). However, a developing literature distinguishes between "impulsive" aggression ("affective, hot") and "predatory" aggression ("planned, profitable and self-controlled, cold"), arguing that impulsive aggression may be most amenable to pharmacotherapy (Connor et al., 2004; Steiner et al., 2003; Vitiello et al, 1990; Vitiello & Stoff, 1997; Jensen et al., in revision). While these subtypes are still nascent in their exact meanings and classification, they may respond to different treatments and lead to different long-term outcomes (Gillberg & Hellgren, 1996). The studies reviewed in this paper fail to discriminate between types of aggression and, therefore, do not address the clinical impact of treatment on different forms of aggression. Nevertheless, we acknowledge that future research must address how this distinction impacts treatment. To this end, the field would benefit from a generally accepted clinical measure of aggression with adequate sensitivity and reliability that could be used in RCTs to help further refine treatment decisions.

The present review suggests that the largest effects for the treatment of pediatric aggression will most likely be seen with MPH for ADHD with co-morbid disruptive behavior problems (mean ES = .90) and risperidone for youth with CD and subaverage IQ (mean ES = .90). Overall, mood stabilizers, SNRIs, antidepressants, and α-2 agonists produced relatively low to medium ES values (range = 0.3 to 0.5) and may be less useful in the management of co-morbid conditions in children.

The large ESs of MPH and risperidone found in this review are relatively powerful clinical effects, and can be better understood in the context of agents used for other disorders. The ESs of MPH and risperidone for aggression are equivalent to those seen in stimulants for ADHD, which are perhaps the strongest treatment improvements observed in child psychiatry. Another revealing contrast is that a meta-analysis of SSRI use for obsessive compulsive disorder (Geller et al., 2003) showed only a moderate ES of 0.46 (combined n = 1044, mean age ages 6-19 years, 2 studies). Further, in a study of adolescents with depression, treatment with fluoxetine and cognitive behavioral therapy (CBT) produced an ES of 0.98, while fluoxetine alone was 0.68 and CBT alone was 0.03 (March et al., 2004). Thus, compared with agents used for other conditions, certain medications may have large clinical effects on impulsive aggression. Given the heterogeneity inherent in early onset maladaptive aggression, however, pharmacotherapy should never be the sole treatment provided to the patient.

The conclusions that can be drawn from this review on the pharmacotherapy of aggression are limited by the quality and breadth of the existing literature. The pool of available data was constrained by a clear publication bias for positive studies which prevented us from exploring all study findings on aggressive behavior. Furthermore, RCTs on newer atypical agents and combined medication regimens were notably lacking in the existing literature. Important treatment issues regarding diagnosis may have also been obscured, as we grouped studies by medication class in order to review the existing RCT data on aggression.

From a clinical perspective, RCTs meeting review criteria do not reflect conditions encountered in "real-world" treatment settings. While psychotropic agents are often administered over the course of several months and years, the average duration of RCTs reviewed in this paper was less than 6 weeks. Also, treatments for aggressive adolescents remain largely understudied, as most trials focused young clinical samples (average age = 10.5 years). The limited population sample was particularly apparent in studies of lithium, which only included inpatients with severe symptoms. Furthermore, it was difficult to assess the effect of medication treatments on aggression because of the lack of valid measurement scales.

Conclusion

Clinically significant pediatric aggression is particularly difficult to treat because it is associated with such diverse primary diagnoses as CD, ADHD, AUT, depression, and MR. Therefore, optimal treatments are multidimensional, encompass both pharmacological and psychosocial treatments, and acknowledge the role of caregivers, family, school, peers, and society at large (Pappadopulos et al., 2003). A growing literature reveals that several medications can be effective in the treatment of aggression, with varying efficacy and ESs. While clinicians rely heavily upon the use of diverse medications to treat aggression, the evidence to support these practices are limited in terms of their inadequate measurement of aggression, young sample sizes, and varying diagnoses. Further RCTs that address these issues and routinely publish ES values are needed to enhance the clinical interpretation of research findings. Overall, the field appears to be making progress in the treatment of persistent and severe aggression in youth. This agenda may be accelerated if the aforementioned suggestions are incorporated into the current research in child psychiatry.

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