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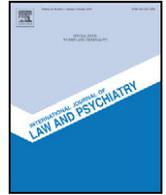


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Pharmacotherapy of impulsive aggression: A quality comparison of controlled studies

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ABSTRACT

The present study assessed the quality of pharmacotherapy trials to treat impulsive aggressive behavior. While a search of the literature found 55 peer-reviewed published studies on the pharmacotherapy of aggression, only 23 met criteria for inclusion in the quality analysis. To be included in this review, the study must have had at least one comparison group to control for placebo effects. The study must have also adequately defined and diagnosed the presence of impulsive aggression or intermittent explosive disorder. The primary reason studies were excluded from the quality analysis was that impulsive aggression was not specifically defined as the behavior being treated (25 of 32, 78%). The results of the quality analysis found that higher quality studies ($n = 10$; 45%) were characterized by a clear definition of impulsive aggression; specific criteria for what constitutes an impulsive aggressive act; the exclusion of participants with neurological disorders, serious mental disorders, and/or low IQ; and information concerning the serum levels of the medication being investigated. A significant weakness found in the literature is the paucity of high quality studies accessing the efficacy of pharmacological agents other than anticonvulsants for the treatment of impulsive aggression.

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1. Introduction

Aggressive behavior is one of the most prevalent concerns in the clinical setting and presents as a symptom of numerous psychiatric and neuropsychiatric disorders. In addition, aggressive behavior without comorbid psychopathology may present as a significant problem in clinical

patients (Houston, Stanford, Villemarette-Pittman, Conklin, & Helfritz, 2003). Research on aggression and violence has consistently recognized two subtypes of aggressive behavior: an impulsive type and a premeditated type.

Impulsive aggression is typically described as an emotionally charged aggressive response characterized by a loss of behavioral control (Barratt, Kent, Bryant, and Felthous, 1991). This type of aggressive display has also been referred to in the literature as affective (Raine et al., 1998) or reactive (Dodge & Coie, 1998) aggression. Specifically, Barratt et al. (1991)

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described it as “a hair trigger response to a stimulus that results in an agitated state and culminates in an aggressive act; during the agitated state...information processing appears to be inefficient.”

No single medication is FDA approved for the treatment of impulsive aggression, yet a number of drugs representing a variety of classes of medication are used for this purpose. Because results of studies on drug efficacy are so inconsistent, it has been difficult to arrive at firm conclusions about the efficacy of individual drugs. Also recognized, however, is the variable quality of such studies. When comparing results, judging the quality of each study is essential. Discrepant results in demonstrated drug efficacy may be explained by differences in study design or quality. To date, reviews of antiaggressive drug trial have either addressed drug efficacy with little attention given to quality of the studies, or the reviews have been concerned with only one particular class of drugs such as anticonvulsants/mood stabilizers (e.g., Jones, Arlidge, Gillham, Reagu, et al., 2011).

Perhaps one of the most frequent flaws in otherwise reasonably designed studies and reviews of the pharmacotherapy of clinical aggression is the failure to recognize that subtypes of aggression exist (e.g., impulsive aggression). A number of book chapters and scientific articles on the pharmacotherapy of aggression either fail to specify the type of aggression being treated, or if the aggression is qualified as impulsive, an adequate definition is not provided. Barratt and Slaughter (1998) identified this as a major problem in the scientific literature on the pharmacotherapy of aggression. This has continued to be an oft repeated error in both individual studies and study reviews.

Inadequate diagnostic criteria and imprecise diagnoses have long confounded research on the treatment of mental disorders. The need for sufficient objective criteria for the diagnosis of mental disorders was the motivation for the development of the Feighner et al. criteria (1972) for common but serious mental disorders, the research diagnostic criteria (Spitzer, Endicott, & Robins, 1975), and the polythetic diagnostic method which dramatically transformed the Diagnostic and Statistical Manual in its Third Edition (American Psychiatric Association, 1980). Within this latter taxonomy, intermittent explosive disorder (IED) first appeared (American Psychiatric Association, 1980), giving clearer and more objective criteria than emotionally unstable personality of the first DSM (American Psychiatric Association, 1952); explosive personality of DSM II (American Psychiatric Association, 1968); or emotionally unstable personality disorder, impulsive type and borderline type of the International Classification of Diseases (ICD 10, World Health Organization, 1991). While IED was carried over into subsequent editions of the DSM (American Psychiatric Association, 1987, 1994, 2000), impulsive aggression was increasingly defined and recognized apart from but taking into account the research supporting IED (e.g., Felthous, Bryant, Wingerter, & Barratt, 1991).

One reason for the continued recognition of impulsive aggression as a separate but overlapping condition with IED is that in earlier editions of the DSM (American Psychiatric Association, 1980, 1987), generalized impulsivity was an exclusionary criterion for IED. However, generalized impulsivity can and often does coexist with impulsive outbursts of physical aggression (Stanford et al., 2003). In the current edition, DSM-IV-TR (American Psychiatric Association, 2000), generalized impulsivity is no longer an exclusionary criterion.

A second and continuing reason for preserving the diagnosis of impulsive aggression is the recognition of its common co-morbidity with borderline, antisocial, and other personality disorders (Houston et al., 2003), whereas the DSM criteria for IED discourage making the diagnosis where the same phenomenon occurs with a personality disorder (American Psychiatric Association, 2000). Even with the diagnostic options of IED, impulsive aggression, and 20 years after Barratt et al.'s (1991) caveat about the importance of correct characterization of the aggressive behavior being examined, studies and reviews on the pharmacotherapy of aggression fail to adequately define the condition for which a drug is given in an experimental trial.

Noting the inconsistent findings in anti-aggression drug trials with phenytoin in particular, Barratt et al. (1991) and Barratt, Stanford, Felthous, and Kent (1997) identified the following failures in quality of investigations that may have led to the discrepant results: failure to exclude subjects with psychiatric or neurological disorders that were identified with objective criteria, or subjects who were taking other medications; failure to control for intelligence levels and different drug serum levels; and reliance on only self-report or subjective observation rather than “well defined behavioral increases of aggressive acts as criteria measures” (Barratt et al., 1997, p. 22). The present systematic review examines these and other parameters of quality in drug trials in order to distinguish studies of higher quality, regardless of whether the study results support efficacy of the drug(s) being studied in the treatment of impulsive aggression.

In addition to the factors identified by Barratt as lacking in drug trials for the treatment of impulsive aggression, this review includes other common measures of quality in drug trials, especially for psychotropic drugs. Through the winnowing of high quality research from less rigorous studies, the best evidence for drug efficacy may emerge with more consistent findings that support sound clinical decisions in selecting therapeutic agents.

Huwiler-Müntener developed a 30 item instrument, the 1996 Consolidated Standards of Reporting Trials (CONSORT) statement (Begg, Cho, Eastwood, Horton et al., 1996) that was designed to assess the quality of drug trials in general (Huwiler-Müntener, 2000; Huwiler-Müntener, Jüni, Junker, & Egger, 2002). Other scales have been developed to measure quality of drug trials (Chalmers et al., 1981; Jadad et al., 1996) including a 2001 version of the CONSORT (Moher, Jones, LePage & COSORT Group, 2001a; Moher, Schulz, Altman & CONSORT Group, 2001b). The original 1996 CONSORT has been utilized by several journals apparently with improved quality of drug trial reporting (Moher et al., 2001a). The 1996 CONSORT has been advanced as useful in assessment of *methodological* quality in particular (Huwiler-Müntener et al., 2002).

For the present comparison, we developed a quality review instrument that like the 1996 CONSORT focuses on quality. This includes critical parameters of the 1996 CONSORT, but also items identified by Barratt et al. (1991, 1997) and Jadad et al. (1996) as items that are needed to assess for the quality of drug trials in treatment of impulsive aggression in particular.

Classes of medications, which have been used to treat impulsive aggression and IED, and have tested for efficacy with controlled trials include: anticonvulsants, mood stabilizers, selective serotonin reuptake inhibitors, and beta adrenergic blockers. This review examined the quality of individual trials of specific agents within each of these categories, for only those controlled studies with an adequate diagnosis of impulsive aggression/IED, and rated the quality of each study based upon quality parameters – most of which are used to assess the general quality of drug trials. Additionally, this review looked for study recognition of potential biological markers that appear to respond to drug treatment contemporaneously with subsidence in aggressive behavior.

2. Concern

A concern for drug trial studies in general and for reviewers of such studies is the tendency to include only those studies with positive results. This bias towards reporting positive results with a net effect of Type I errors can exist with the individual investigators, the drug industry that finances drug trials, the peer review and editorial processes in selecting reports for publication and in reviews of drug trial studies. Also known as the “file drawer problem” (Rosenthal, 1979), this bias in the science and publication of drug trials has been especially studied and discussed in the context of peer review and editorial selection of drug trial reports for publication (Callahan, Wears, Weber, Barton, & Young, 1998; Dickerson, 1990; Greenwald, 1975; Mahoney, 1977; Olson et al., 2002;

Rosenthal, 1979; Sackett, 1979; Smith, 1980; Sterling, 1959). For this review, we made a point of including all studies of threshold relevance and quality regardless of the positivity or negativity of study results.

3. Methods

3.1. Selection of drug trial studies

Using MEDLINE and PsycINFO, the authors attempted to identify all controlled studies in the English language that tested for drug efficacy in the pharmacotherapy of aggression. The present article did not include studies in the pharmacotherapy of acute agitation on an emergency basis, but rather the ongoing administration of a medication in order to prevent or reduce the frequency and intensity of future acts of aggression. To be included in this review, the study must have at least one control or comparison group to control for placebo effect. The study must have adequately defined and diagnosed the presence of impulsive aggression by approximating the definition of impulsive aggression provided by Barratt et al. (1991, 1997), applying the criteria for IED from one of the DSMs since the third edition, or a (reasoned) modification of such criteria.

3.2. Assessment of quality: Checklist

A 19-item quality checklist was developed by the authors using items identified by Barratt et al. (1991, 1997), and the 14 items for which at least three (out of five) judges in Jadad et al. (1996) used to rate the quality of reports of randomized clinical trials. All items used to assess the quality of drug trials in the treatment of impulsive aggression are listed in Table 4.

Although some quality measures are clearly either fully present or fully absent, others can exist in various degrees, for example, the description of inclusion and exclusion criteria. Therefore weighted points were given to each item, with 0 = the item is absent from the study, 1 = the item is present, 2 = the item is present to a satisfactory degree, or 3 = the item is present to a highly satisfactory degree. Dichotomous quality measures (e.g., random allocation) which were either present or absent were scored 0 = the item is absent or 3 = the item is present. Total scores on the quality checklist can range from 0 to 57.

3.3. Assessment of quality: Process

Two doctoral graduate students in psychology, both co-authors of this article, were first familiarized with the checklist items. Each methodically examined each study independently and rated the individual items. After each study was rated, the results of the two ratings were compared for consistency and the scores averaged for a total score on each item.

3.4. Analysis of results

Interrater reliability was calculated for the scores of the two independent raters using an intraclass correlation for consistency. Based upon the median score of all items used to assess study quality, each study was rated as higher (above the median) or lower (at the median and below) quality. Finally, statistical analyses were applied to higher and lower quality studies to determine on which criteria they differed.

4. Results

4.1. Selection of drug trial studies

Literature searches for studies assessing drug efficacy in the pharmacotherapy of aggression found 55 peer-reviewed publications. A review of those studies found that 23 met criteria for inclusion in

the quality comparison. The primary reason studies were not included in the quality comparison was that they did not specifically assess impulsive aggression but evaluated aggression in general (Table 1).

4.2. Interrater reliability

Comparison of the quality scores for the two independent raters found that they were highly consistent with an intraclass correlation of 0.93.

4.3. Assessment of quality

One of the 23 studies included in the quality comparison (Leiberich, Nickel, Tritt, & Pedrosa Gil, 2008) was a follow-up study of another (Tritt et al., 2005), thus the two were treated as a single study. The average quality score for the 22 studies was 41.3 (SD 6.6). The median and mode were both 42.0. Anticonvulsants were by far the most common pharmacological agents studied in the treatment of impulsive aggression, comprising 14 of the 22 studies. Quality scores for the anticonvulsant studies are presented in Table 2 while quality scores for the remaining studies are presented in Table 3.

Ten studies had a quality scores above the median and were classified as higher quality while the remaining 12 studies were classified as lower quality. Statistical comparison between higher and lower quality studies on the checklist items were done using *t*-tests and are reported in Table 4.

5. Discussion

The present study assessed the quality of pharmacotherapy trials to treat impulsive aggressive behavior. While a search of the literature found 55 published studies on the pharmacotherapy of aggression, only 23 met criteria for inclusion in the quality analysis. The primary reason studies were excluded from the analysis was that impulsive aggression was not specifically defined as the behavior being treated (25 of 32, 78%). This demonstrates a significant general weakness in the aggression pharmacotherapy literature.

As described earlier, physical aggressive behavior has traditionally been classified into two distinct subtypes (McEllistrem, 2004; Stanford et al., 2003): (a) an emotionally charged, uncontrolled type of aggressive display (impulsive, hostile, affective, and reactive) or (b) a planned, controlled, unemotional aggressive act (premeditated, instrumental, predatory, and proactive). Significant differences in neurochemistry, psychophysiology, cognitive functioning and response to treatment/intervention have been shown between these aggressive subtypes (Barratt et al., 1997; Houston et al., 2003). This makes the careful characterization of aggressive behavior imperative when assessing treatment effectiveness. Presently, a majority of the pharmacotherapy of aggression literature appears to have ignored this distinction making the determination of efficacy for many medications in the treatment of aggressive behavior difficult if not impossible.

The results of the quality analysis found that higher quality pharmacotherapy studies are characterized by a clear definition of impulsive aggression, specific criteria for what constitutes an impulsive aggressive act, the exclusion of participants with neurological disorders, serious mental disorders and/or low IQ, and information concerning the serum

Table 1
Reasons studies were excluded from quality comparison.

Reason	<i>n</i>	% of total
Not specifically impulsive aggression	25	78.1%
Case study	3	9.4%
Open trial	2	6.3%
Retrospective chart review	1	3.1%
Single administration	1	3.1%

Table 2
Quality of anticonvulsant trials in the treatment of impulsive aggression.

Study	Medication	Population	Gender	Quality score
Houston and Stanford (2006)	Phenytoin	Community sample	M	51.0
Stanford et al. (2005)	Phenytoin Carbamazepine Valproate	Community sample	M	51.0
Barratt et al. (1997)	Phenytoin	Prison inmates	M	48.0
Stanford et al. (2001)	Phenytoin	Community sample	M	48.0
Cueva et al. (1996)	Carbamazepine	Children (5–12 years old)	M/F	45.5
Hollander et al. (2003)	Divalproex	Psychiatric outpatients	M/F	45.5
Barratt et al. (1991)	Phenytoin	Prison inmates	M	44.0
Mattes (2008)	Levetiracetam	Psychiatric outpatients	M/F	43.0
Mattes (2005)	Oxcarbazepine	Psychiatric outpatients	M/F	42.0
Donovan et al. (2000)	Divalproex	Children (10–18 years old)	M/F	41.5
Hollander, Swann, Coccaro, Jiang, and Smith (2005)	Divalproex	Psychiatric outpatients	M/F	38.0
Tritt et al. (2005), Leiberich et al. (2008)	Lamotrigine	Community sample	F	38.0
Gardner and Cowdry (1986)	Carbamazepine	Psychiatric outpatients	F	35.0
Foster, Hillbrand, and Chi (1989)	Carbamazepine	Forensic patients	M	25.0

levels of the medication being investigated. Higher and lower quality studies both showed weaknesses in the reporting of power, following-up participants after the study ended, and the inclusion of biological markers as outcome measures (Table 4). These results call into question the reliability of the data from those studies characterized as lower quality and demonstrate the need for a standardized approach to the assessment of pharmacological agents in the treatment of impulsive aggressive behavior.

A significant problem in the literature is the paucity of studies accessing the efficacy of pharmacological agents other than anticonvulsants for the treatment of impulsive aggression. Anticonvulsant agents have been widely researched with a majority of those studies

Table 3
Quality of drug trials in the treatment of impulsive aggression.

Study	Medication	Population	Gender	Quality score
Lithium				
Campbell et al. (1995)	Lithium	Children (5–12 years old)	M/F	44.0
Campbell et al. (1984)	Lithium	Children (5–12 years old)	M/F	42.0
Sheard, Marini, Bridges, and Wagner (1976)	Haloperidol Lithium	Prison inmates	M	42.0
Fluoxetine				
Lee, Kavoussi, and Coccaro (2008a)	Fluoxetine	Intimate partner abusers	M	43.5
Coccaro, Lee, and Kavoussi (2009)	Fluoxetine	Psychiatric outpatients	M/F	42.0
Coccaro and Kavoussi (1997)	Fluoxetine	Psychiatric outpatients	M/F	37.5
Other drugs				
Amery, Minichiello, and Brown (1984)	D-amphetamine	Children (8–11 years old)	M	30.5
Greendyke and Kanter (1986)	Pindolol	Brain injured patients	M/F	31.0

Table 4
Comparison of quality checklist items between higher and lower quality studies.

Quality checklist items	Higher quality (n = 10)	Lower quality (n = 12)	p
Measures of aggression			
a) Impulsive aggression adequately defined	2.60 (0.70)	1.92 (0.73)	0.04
b) Behavioral measures of aggressive acts	2.85 (0.24)	2.71 (0.33)	0.26
c) Criteria for impulsive aggressive acts	2.75 (0.49)	1.88 (1.09)	0.02
d) Intent to treat aggression	2.80 (0.42)	2.33 (0.81)	0.10
Recruitment of participants			
a) Clear inclusion criteria	2.95 (0.16)	2.50 (0.71)	0.53
b) Exclusion criteria			
1. Neurological disorders	2.95 (0.16)	1.79 (1.09)	0.00
2. Serious DSM Axis I mental disorders	2.70 (0.67)	1.83 (1.01)	0.03
3. Low IQ	2.20 (1.25)	0.92 (1.04)	0.02
4. Other psychotropic medications	2.40 (0.70)	1.67 (1.23)	0.09
Study design			
a) Clear hypothesis and objectives	2.90 (0.32)	2.75 (0.45)	0.37
b) Randomization ^a	3.00 (0.00)	2.75 (0.87)	0.34
c) Blind ^a	3.00 (0.00)	3.00 (0.00)	–
d) Multiple observers ^a	2.70 (0.63)	2.50 (0.67)	0.48
e) Power reported ^a	1.00 (1.41)	0.25 (0.87)	0.17
Outcome measures			
a) Clear/validated outcomes	3.00 (0.00)	2.92 (0.19)	0.17
b) Description of withdrawals and dropouts	2.60 (0.81)	2.42 (0.95)	0.63
c) Adequate follow-up	0.45 (0.72)	1.17 (1.27)	0.11
d) Biological markers ^a	0.90 (1.45)	0.50 (1.17)	0.49
e) Serum levels reported	2.60 (0.94)	1.25 (1.23)	0.01

Bolded p-values indicate items which were significantly associated with the higher quality studies.

^a Denotes dichotomous item.

characterized as higher quality (Table 2). It is clear from the literature that several anticonvulsant agents are effective in the treatment of impulsive aggressive outbursts (Stanford, Anderson, Lake, & Baldrige, 2009). Unfortunately, this cannot be said for most other pharmacological agents. Only a limited few have been assessed and most of those studies were characterized as lower quality in the present analysis (Table 3). It is hoped that this study will serve as a call to aggression researchers to redouble their efforts in the investigation of pharmacological agents such as selective-serotonin reuptake inhibitors, lithium, and atypical antipsychotics for the treatment of impulsive aggressive behavior.

Most reviews of drugs used to treat aggressive behavior do not methodically evaluate the quality of drug trials. An exception is the meta-analysis by Jones, Arlidge, Gillham, Reagu et al. (2011). The aim of this meta-analysis was to assess the evidence for efficacy of mood stabilizers in reducing aggression that was repetitive or impulsive. The investigators cast a broad net and identified 52 drug trials for treating aggression, but only eight reports, representing ten studies, contained enough information to use in the meta-analysis. Using the Jadad Scale (Jadad, Moore, Carroll et al., 1996), to assess for risk of bias, eight had Jadad scores of three or higher. From their analysis, only three of these studies included intention to treat analysis. Evidence supported efficacy for carbamazepine/oxcarbazepine, phenytoin and lithium, but not all mood stabilizers. Levetiracetam and valproate were shown to be not effective.

In comparing the meta-analysis by Jones and colleagues with the present systematic review, some differences should be noted. The focus of the Jones meta-analysis was drug efficacy, but using some measures of quality to measure bias. The emphasis of the present review was comparing the quality of the drug trials regardless of positive or negative outcome. Parameters were intended to assess methodological quality, not reporting quality which is more the concern of the Jadad Scale. The present study sought studies that convincingly targeted impulsive aggression, adequately defined and diagnosed. Recurrent aggression that is not also impulsive would not have qualified. The present study was open to the trial of adequate quality of any drug, not just mood stabilizers.

The present study, though targeting impulsive aggression, did not exclude any demographic groups. Thus, it was not limited to drug trials in adult subjects, but also in children. The reader must bear in mind the possibility of children responding differently than adults to some drugs. In addition, children are more likely to have a primary diagnosis of attention deficit hyperactivity disorder which can include impulsive aggression but includes other symptoms as well. Similarly, some adults who are treated for impulsive aggression may actually have adult ADHD and their other symptoms of ADHD may not be registered in the study. Future investigations can disentangle pure impulsive aggression from that associated with ADHD and then test for differential responses to presumed anti-aggressive drugs and psycho-stimulants.

6. Conclusions

Critical to improving pharmacotherapy of clinical aggression is satisfactory methodologic quality. This requires not only accurate and unbiased measuring but also an adequate definition and diagnosis of the condition that is to be measured. With compelling, replicated research that impulsive but not premeditated aggression is amenable to pharmacotherapy (e.g., Barratt et al., 1997), the first step in research design is to distinguish impulsive aggression and determining how its intensity and frequency is to be monitored. Other parameters of quality are basically those used to assess quality of trials of drugs in general, but with some considerations specific to the study of aggression.

Most of the higher quality studies (i.e., those with a score above the median) were anticonvulsants. All of these well tested anticonvulsants with the exception of levetiracetam were shown to be efficacious. Evidence from studies of satisfactory methodologic quality supports the efficacy of phenytoin, carbamazepine, valproate/divalproex in treating impulsive aggression. Of the drug trials involving non-anticonvulsant drugs, the quality of the trials with lithium and fluoxetine are most satisfactory, and the individual trials of these drugs shows them to be efficacious.

The present results suggest that the reliability of a majority of the pharmacotherapy of aggression studies presently in the literature is questionable. The authors suggest that three methods are desperately needed in future pharmacotherapy studies of aggression to overcome the present shortfall: careful characterization of aggressive behavior into subtypes, the use of a standard approach to the assessment of treatment efficacy, and the investigation of a wide range of pharmacological agents.

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