Pharmacotherapy for the Treatment of Aggressive Behavior in General Adult Psychiatry: A Systematic Review

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Objective: To systematically review the evidence for pharmacologic management of outwardly directed aggressive behavior in general adult psychiatry.

Data Sources: Literature searches in PubMed, EMBASE, PsycINFO, and Cochrane libraries from 1966 through March 2005 were used to identify relevant studies. The keywords *aggression*, *violence*, *anger*, and *hostility* combined with *drug therapy*, *psychotropic drugs*, *adrenergic β-antagonists*, *anticonvulsants*, *antidepressants*, *antipsychotic agents*, *benzodiazepines*, and *lithium* were searched. Furthermore, the retrieved publications were searched for additional references.

Study Selection: All randomized controlled trials addressing pharmacotherapy for aggression or aggression-related symptoms were included, except studies addressing the "emergency situation" and studies conducted in specialized psychiatric or non-psychiatric settings.

Data Extraction: Evidence synthesis was performed using the "best-evidence principle." Two authors independently adjudicated methodological quality and generalizability to daily clinical practice.

Data Synthesis: Thirty-five randomized controlled trials met the inclusion criteria and were evaluated. On the basis of a best-evidence synthesis model, weak evidence for antiaggressive effects of antipsychotics, antidepressants, anticonvulsants, and β-adrenergic–blocking drugs was found. Atypical antipsychotics appeared superior to typical antipsychotics. The use of various outcome measures and insufficient data reporting in the individual studies hampered the quantitative assessment of efficacy across studies. Further limitations of the available randomized controlled trials included small sample sizes, short study duration, and poor generalizability to daily clinical practice setting.

Conclusions: Whereas pharmacotherapy is frequently applied in aggressive patients, only weak evidence of efficacy of various drug classes was found. Consensus about the use of aggression measurement scales in clinical trials is necessary for future research. Furthermore, large-scale trials with more naturalistic designs, as opposed to classical randomized controlled trials with strict inclusion and exclusion criteria, may be advisable in order to obtain results that are more generalizable to daily clinical practice.

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In mental health care, aggression is an important issue, with, for example, an incidence of 9.3 incidents per bed per year in Europe at acute admission wards.[1] Besides high costs,[2] aggression influences therapeutic environment and well-being of both patients and staff workers.[3,4] In a recent study conducted in East London, more than 1 out of every 5 psychiatric nurses reported that they had not been able to go to work owing to workplace violence during the preceding year.[5] Although far less investigated, aggression also appears to be a common phenomenon in psychiatric outpatients.[6]

Given the incidence and impact of aggression, management of aggression has high priority in mental health care. Most aggressive incidents occur during the first week following admission.[7] In a small proportion of patients, aggression will remain an ongoing problem.[8–10]

Several interventions are used to manage aggressive behavior, including cognitive therapy and training of nursing staff in the case of hospitalized patients.[11–13] Pharmacotherapy is also frequently used in aggressive patients.[14] Several drugs, including anticonvulsants, antipsychotics, and antidepressants, have been used for repetitively aggressive patients.[11,12] A small number of systematic reviews have evaluated the evidence for the use of these drugs.[15–17] However, the most recent reviews investigating the evidence for efficacy of pharmaco-

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therapy for the ongoing management of aggression in psychiatric patients date from 1996 and 1997.[15,16] In these reviews, clinical trials as well as case reports were included. To our knowledge, a systematic review on this subject based upon randomized controlled trials (RCTs)—considered as the gold standard to obtain evidence[18]—never has been conducted. The objective of this review is to systematically review the literature for the evidence of the pharmacologic management of aggression in repetitively aggressive patients in general adult psychiatry, restricting ourselves to RCTs. Randomized controlled trials have some limitations as well, e.g., strict inclusion and exclusion criteria, which are likely to reduce the generalizability to daily clinical practice[19]; we also intended to assess the generalizability of the evidence.

METHOD

Data Sources

A literature search was conducted within the PsycINFO, EMBASE, Cochrane, and PubMed databases from 1966 through March 2005 to identify published RCTs, systematic reviews, and meta-analyses assessing the efficacy of drugs for the management of aggression or aggression-related symptoms, including violence, hostility, and anger. As main search terms, we used MeSH terms, covering the words *aggression*, *violence*, *anger*, and *hostility* combined with *drug therapy*, *psychotropic drugs*, *adrenergic β-antagonists*, *anticonvulsants*, *antidepressants*, *antipsychotic agents*, *benzodiazepines*, and *lithium*. Furthermore, the retrieved publications were searched for additional references.

Study Selection

Studies were eligible for inclusion in this review if they met the following criteria: (1) random allocation to treatment, as mentioned in the study; (2) the study population consisted of adult (aged between 18 and 65 years) general psychiatric patients in whom aggression might be an ongoing problem. Studies applying to specialized psychiatric settings—like child psychiatry, mental retardation, and organic brain diseases—or to nonpsychiatric settings—like prisons—were excluded; (3) outwardly directed aggression or aggression-related symptoms were either a primary or secondary outcome in the study; (4) the study did not address pharmacotherapy of aggression or aggression-related symptoms in the "emergency" situation; (5) a previously published scale was used to measure aggression or aggression-related symptoms; (6) the study was English language and published in a peer-reviewed journal before March 2005; and (7) the study drug under investigation is currently registered by the U.S. Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMEA).

One reviewer (L.E.G.) screened abstracts to determine whether studies should be included in the review. In case of any doubt, the full paper was retrieved. If there was still any doubt, the study was judged by a second reviewer (E.R.H. or J.J.S.).

Data Extraction

Trials were categorized into subgroups according to therapeutic drug class. For every subgroup, evidence of efficacy was determined. Because effect sizes were difficult to compute owing to the use of a variety of continuous outcome scales, evidence of efficacy was determined using the best-evidence synthesis principle.[20] The best-evidence synthesis method used in this review is based on the model of van der Windt et al.[21] In this model, studies are weighted according to methodological quality, clinical relevance, and statistical significance. Distinction was made between insufficient, weak, and strong evidence of efficacy or evidence of no efficacy, using decision rules presented in Figure 1.[22]

Using this method, at least 3 studies assessing the drug are required to obtain weak or strong evidence of efficacy.

Quality Assessment

The Jadad scale (scores range from 0 to 5) was used to adjudicate the methodological quality of the studies.[23] Two reviewers performed this assessment independently (L.E.G. and E.R.H. or J.J.S. or T.C.G.E.). Interrater agreement was calculated using the kappa statistic. Subsequently, disagreement was discussed and resolved. Studies with Jadad scores of 3 or more were rated as having an acceptable methodological quality.

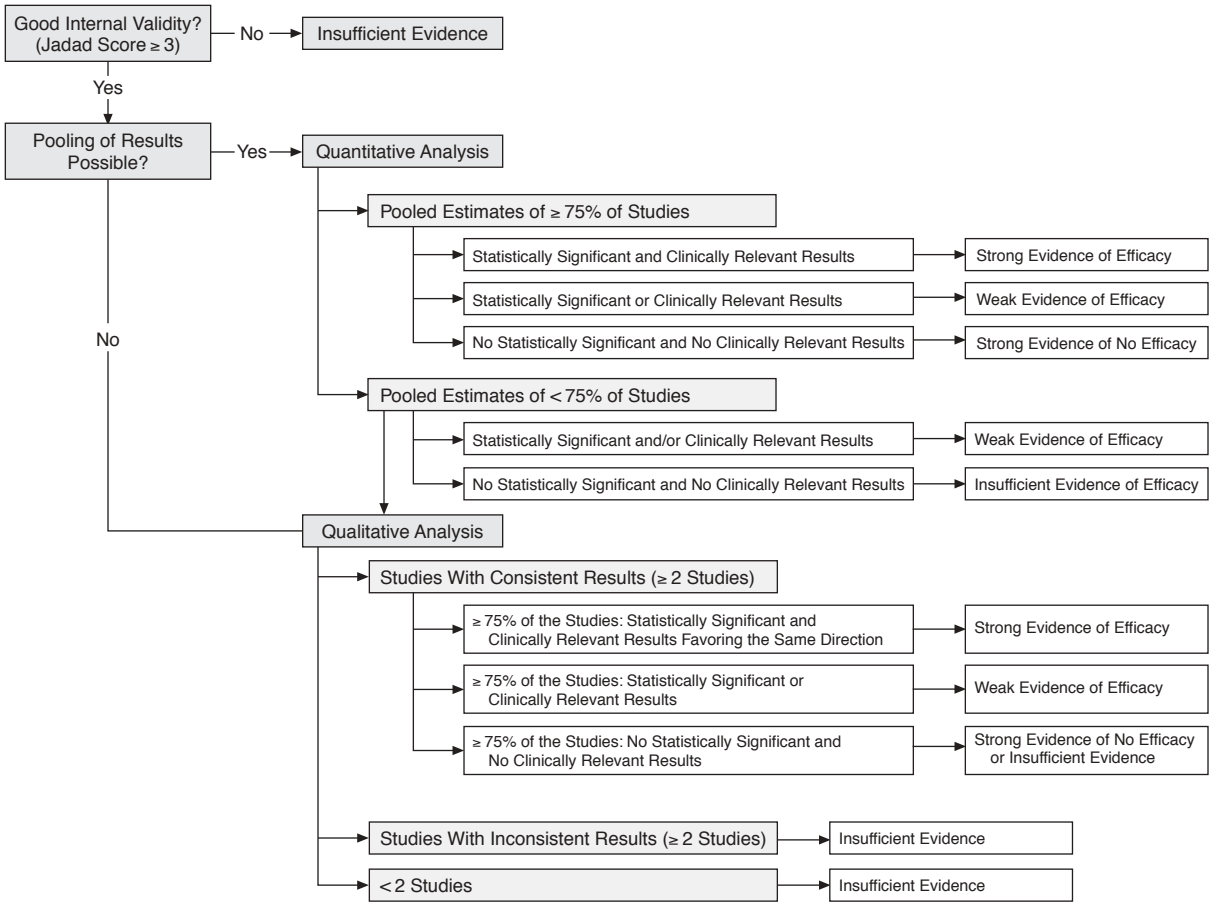
Quantitative Data Synthesis

Effect sizes were expressed as standardized mean difference (SMD).[24] The SMD was interpreted as described by Cohen[25] and applied using the following effect sizes: small 0.2, medium 0.5, and large 0.8. The SMD can only be applied to normally distributed data. In case of skewed data, the SMD cannot be computed. We investigated skewness by dividing mean through standard deviation; a value of less than twice the standard deviation was indicative of skewed data.[26]

Study Generalizability

To our knowledge, no validated checklists or methods to rate generalizability to daily clinical practice are available. Therefore, we defined our own criteria. Generalizability was defined as the probability that aggressive patients as seen in daily clinical practice would be included in the study. Generalizability was scored on a scale from 1 to 5, where studies with a score of 3 or more were considered to have an acceptable generalizability. To generate this score, the following 2 items were consid-

Figure 1. Best-Evidence Synthesis[a]



[a]Adapted with permission from Smidt et al.[22]

ered: (1) The source population is representative for psychiatric patients seen in daily clinical practice and (2) No inclusion or exclusion criteria that could exclude typical aggressive psychiatric patients, e.g., a history of drug abuse, violence in the past, or the use of concurrent psychotropics, were applied.

The same 2 independent reviewers who assessed the Jadad scores also assessed the generalizability. Interrater agreement was calculated using the kappa statistic. Subsequently, disagreement was discussed and resolved.

RESULTS

Study Selection

As can be seen in Figure 2, the use of our search terms resulted in the identification of 467 publications. On the basis of the title and the study abstracts, 425 studies were excluded from further analysis; the remaining 42 full papers were retrieved and screened. Reasons for exclusion are shown in Figure 2. Finally, we located 35 RCTs[27–61] describing the effect of different drugs on aggression or aggression-related symptoms.

Study Characteristics

Detailed study characteristics are summarized in Table 1. The study outcomes are displayed in Table 2.

Outcome Measures

A whole range of different outcome measures—21 in total—were used in the RCTs included and involved observational scales as well as self-report scales. Furthermore, some scales were especially designed for measuring aggression, while others were subscales measuring items related to aggression in a broader perspective, for example the anger scale of the Profile of Mood States.[79]

The most frequently used specific aggression scales were different versions of the Overt Aggression Scale (OAS).[62] From the 21 used outcome scales, the OAS modified for outpatients was used more often. Other outcome measures included diagnosis-related scales, like

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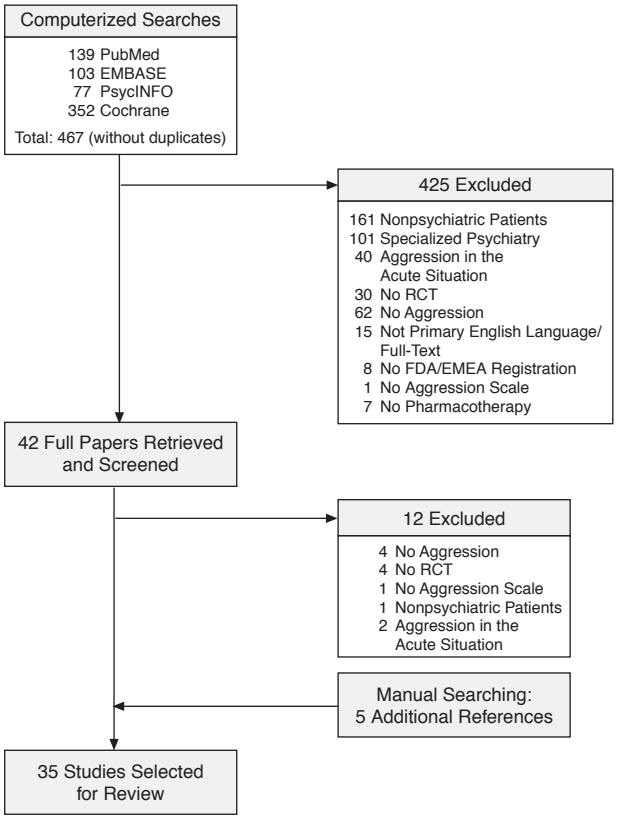
Figure 2. Study Selection



Abbreviations: EMEA = European Agency for the Evaluation of Medicinal Products, FDA = U.S. Food and Drug Administration, RCT = randomized controlled trial.

subscales of the Positive and Negative Syndrome Scale (PANSS)[63] and the Borderline Personality Disorder Severity Index (BPDSI).[64]

Patients

Most studies were conducted in a schizophrenic population* or cluster B personality disordered patients.† The other diagnoses included posttraumatic stress disorder (PTSD),[35,45,58] autistic disorder,[44] intermittent explosive disorder,[43] attention-deficit/hyperactivity disorder,[29] anorexia nervosa,[38] and depressive disorder.[36,39,41] Of the 35 studies, 15 were conducted in a population solely consisting of outpatients.‡

Follow-Up

The follow-up period ranged from 3 to 24 weeks. In the majority of studies,§ the follow-up period was 6 to 12 weeks, while 7 studies‖ had a long-term follow-up (> 12 weeks) and 9 studies¶ had a short-term follow-up (< 6 weeks).

Control Group

Of the 35 RCTs, 27 compared active drug(s) to placebo. The other studies# used an active drug as control. Of the 35 RCTs included in this review, 33 were double blind and 2 were not.[38,43] In 3 studies,[29,32,52] a crossover design was used. In one study,[43] the outcome measurement was assessed single blind.

Quality Assessment

In 31 of the 35 RCTs, the methodological quality was judged acceptable as reflected by a score on the Jadad list of 3 or more. The 4 studies with a Jadad score of less than 3[28,38,39,43] were excluded from the evidence synthesis. Interrater agreement for the Jadad score was good (kappa statistic = 0.73).

Generalizability

Generalizability to daily clinical practice was judged to be acceptable for 20 of the 35 studies (Table 2). Several factors contributed to poor generalizability. In most studies, eligibility criteria did not comprise a certain baseline level of aggression before the start of the trial, as measured by a scale. This might have contributed to a low baseline level of aggression in some of the studies. Furthermore, current drug abuse, alcohol abuse, or other psychotropic medication use, factors associated with aggression,[14,84] were frequently used as exclusion criteria.**

Furthermore, in many studies, the recruitment method did not favor inclusion of patients for whom aggression appears to be an ongoing problem: in some studies, patients were recruited through advertisement.[40,48,49,53–55] As aggressive patients are less likely to give informed consent, this method might lead to "volunteer bias."[85] In other studies, the source population comprised patients with an acute exacerbation of schizophrenia.[30,31,33,42,59] Acute exacerbation is associated with aggression, especially in the first week of admission; however, once the patient is stabilized, aggression will probably not remain as an ongoing problem.[8] Interrater agreement for the generalizability was good (kappa statistic = 0.60).

Evidence Synthesis for the Different Drug Classes

Evidence of efficacy for the different drug classes, i.e., antipsychotics, antidepressants, anticonvulsants, and β-adrenergic blockers, is displayed in Table 3.

We were not able to calculate the SMD for most of the studies because many studies did not provide the required data. In those studies for which the required data were provided, the distribution appeared skewed.[26] In the latter studies, the SMD can be calculated from log-transformed

* References 27, 28, 30–34, 42, 47, 52, 59–61.
† References 37, 40, 46, 48–51, 53–57.
‡ References 35, 38–41, 45, 46, 48, 49, 53–58.
§ References 27, 28, 32, 35, 38, 39, 41, 42, 44–46, 48, 54–57, 60, 61.
‖ References 29, 34, 40, 47, 49, 52, 53.
¶ References 30, 31, 33, 36, 37, 50, 51, 58, 59.
# References 27, 29, 34, 36, 43, 54, 59, 60.
** References 29, 35, 37, 39–42, 44, 46, 48–50, 53–58.

Table 1. Study Characteristics

Study	Diagnosis	Aggression Before Trial[a]	Exclusion Criteria	Weeks[b]	Drugs: N, N[c]
Antipsychotic agents					
Blin et al[59] 1996	Schizophrenia, acute exacerbation with symptoms of anxiety, inpatients	NAR	Relevant somatic disorder, history of drug or alcohol abuse during past year, schizoaffective disorder, use of long-acting antipsychotics	4	Haloperidol: 20, 14 Risperidone: 21, 17 Methotrimeprazine: 21, 14
Citrome et al[34] 2001	Schizophrenia/schizoaffective disorder: treatment resistant to previous neuroleptics, inpatients	NAR	History of treatment resistance to study drugs	14	Clozapine: 40, 32 Risperidone: 41, 28 Olanzapine: 39, 30 Haloperidol: 37, 25
Czobor et al[28] 1995	Schizophrenia, inpatients	PANSS hostility > 2	Comorbid psychiatric disorder, drug or alcohol abuse in the past 6 months, relevant somatic disorder	8	Risperidone: 85, ? Haloperidol: 24, ? Placebo: 30, ?
Marder et al[61] 1997	Schizophrenia, inpatients	NAR	Comorbid psychiatric disorder, drug or alcohol abuse in the past 6 months, relevant somatic disorder	8	Risperidone: 342, 193 Haloperidol: 85, 35 Placebo: 86, 27
Min et al[27] 1993	Schizophrenia, inpatients	NAR	Relevant somatic disorder, drug or alcohol abuse during past year, comorbid psychiatric disorder	8	Risperidone: 16, 13 Haloperidol: 19
Monnelly et al[45] 2003	Combat-related PTSD, outpatients	NAR	History of antipsychotic use, schizophrenia, bipolar disorder, organic mental disorder	6	Risperidone: 8, 7 Placebo: 8, 8
Peuskens[60] 1995	Schizophrenia, inpatients	NAR	Comorbid psychiatric disorder, relevant somatic disorder, history of alcohol or drug abuse in previous 12 months	8	Risperidone: 1136, 856 Haloperidol: 226, 205
Zanarini and Frankenburg[53] 2001	Borderline personality disorder, outpatients	NAR	Relevant somatic disorder, current drug or alcohol abuse, use of psychotropics	24	Olanzapine: 10, 8 Placebo: 9, 4
β-Adrenergic–blocking drugs					
Allan et al[30] 1996	Schizophrenia, male inpatients	NAR	Relevant somatic disorder	3	Nadolol: 17, 16 Placebo: 17, 16
Alpert et al[31] 1990	Schizophrenia, schizoaffective disorder, bipolar disorder, male inpatients	NAR	Relevant somatic disorder	3	Nadolol: 16, 15 Placebo: 16, 16
Caspi et al[32] 2001	Schizophrenia, male inpatients	≥ 4 incidents in 1 month	Relevant somatic disorder	6	Pindolol/placebo: 30, 23; crossover
Maoz et al[42] 2000	Schizophrenia and schizophreniform disease, acute exacerbation, inpatients	NAR	Physical disorder, current drug abuse, depot neurolepticum	8	Propranolol: 18, 18 Placebo: 16, 16
Ratey et al[47] 1992	Schizophrenia, schizoaffective disorder, mentally retarded, inpatients	NAR	Relevant somatic disorder	13	Nadolol: 22, 16 Placebo: 26, 25
Anticonvulsants					
Citrome et al[33] 2004	Schizophrenia, inpatients	≥ 6 points on PANSS subscale	Schizoaffective disorder, mood disorder, current serious violent ideas, relevant somatic disorder	4	Divalproex sodium: 125, 120 Placebo: 124, 122
de la Fuente and Lotstra[37] 1994	Borderline personality disorder, inpatients	NAR	DSM-III-R Axis I disorder, somatic disorder, suspected poor treatment compliance, inability to stop drug or alcohol use	4,5	Carbamazepine: 10, 8 Placebo: 10, 10
Frankenburg and Zanarini[40] 2002	Borderline personality disorder with a comorbid bipolar II disorder, outpatients, women	NAR	Relevant somatic disorder, current drug abuse	24	Divalproex sodium: 20, 20 Placebo: 10, 10
Hollander et al[56] 2003	Cluster B personality disorder, outpatients	≥ 15 points on OAS-M	Psychotic disorder, mood disorder, current drug abuse, relevant somatic disorder	12	Divalproex sodium: 43, 39 Placebo: 48, 46
Hollander et al[55] 2001	Borderline personality disorder, outpatients	NAR	Psychotic disorder, mood disorder, relevant somatic disorder, no other psychotropics (except antidepressants)	10	Divalproex sodium: 12, 6 Placebo: 4, 0
Nickel et al[46] 2005	Borderline personality disorder, male outpatients	NAR	Schizophrenia, major depression/bipolar disorder, other psychotropics, substance abuse	8	Topiramate: 22, 22 Placebo: 22, 20

continued

Table 1. Study Characteristics (cont.)

Study	Diagnosis	Aggression Before Trial[a]	Exclusion Criteria	Weeks[b]	Drugs: N, N[c]
Antidepressants					
Coccaro and Kavoussi[57] 1997	Personality disorder, outpatients	≥ 15 points OAS-M for 1 month	Schizophrenia, mood disorder, delusional disorder, currently drug or alcohol dependent	12	Fluoxetine: 27, 14 Placebo: 13, 9
Davidson et al[36] 1981	Depressed inpatients	NAR	Psychotic disorder, mania, mental retardation, organic brain syndrome	3	Phenelzine: 24, 21 Imipramine: 25, 22
Davidson et al[35] 2002	PTSD, outpatients	NAR	Psychotic disorder, bipolar disorder, major depression, anxiety disorder, organic mental disorder, alcohol or drug dependence or use, relevant somatic disorder, other psychotropics, cognitive-behavioral therapy	12	Sertraline: 194, 191 Placebo: 201, 194
McDougle et al[44] 1996	Autistic disorder, inpatients and outpatients	NAR	Illicit substance abuse, notable medical condition, other psychotropics, psychotic disorder	12	Fluvoxamine: 15, 15 Placebo: 15, 15
Fava et al[39] 1997	Depressed outpatients	NAR	Pregnancy, unstable medical illness, drug abuse, psychotic disorder, bipolar disorder, pregnancy	12	Sertraline: 17, ? Imipramine: 21, ? Placebo: 19, ?
Fassino et al[38] 2002	Anorexia nervosa, outpatients	NAR	Psychiatric comorbidity	12	Citalopram: 26, 19 Placebo: 26, 20
van der Kolk et al[58] 1994	PTSD outpatients	NAR	Schizophrenia, bipolar disorder, drug or alcohol addiction, organic mental disorder	5	Fluoxetine: 33, 21 Placebo: 31, 27
Rinne et al[48] 2002	Borderline personality disorder, outpatients	NAR	No other psychotropics during the trial	6	Fluvoxamine: 20, 16 Placebo: 18, 14
Salzman et al[49] 1995	Borderline personality disorder, outpatients	NAR	History of hospitalization, drug or alcohol abuse, recent suicidal behavior, self-mutilation, use of other psychotropics	13	Fluoxetine: 13, ? Placebo: 9, ?
Vartiainen et al[52] 1995	Schizophrenia, inpatients	≥ 1 incident/month on Staff Observation Aggression Scale for 2 months	Depression, relevant somatic disorder	24	Citalopram/placebo: 19, 14; crossover
Others[d]					
Dorrego et al[29] 2002	Attention-deficit/hyperactivity disorder, inpatients	NAR	Substance abuse, IQ < 75, neurologic disorder, pregnancy	18	Lithium/methylphenidate: 32, 23; crossover
Lipman et al[41] 1986	Depressive and anxiety disorder, outpatients	NAR	Drug or alcohol addiction, mental retardation, psychosis, bipolar disorder	8	Imipramine: 149, 103 Chlordiazepoxide: 140, 95 Placebo: 136, 87
Mattes[43] 1990	Intermittent explosive disorder, inpatients	NAR	Diagnoses requiring other treatment	Unclear	Carbamazepine: ?, 22 Propranolol: ?, 29
Soloff et al[51] 1989	Borderline personality disorder, inpatients	NAR	Schizoaffective disorder, schizophrenia, mania, hypomania	5	Haloperidol: 31, 28 Amitriptyline: 30, 29 Placebo: 29, 28
Soloff et al[50] 1993	Borderline personality disorder, inpatients, follow-up partly following admission	NAR	Drug or alcohol dependence, seizures, mental retardation	5	Haloperidol: 36, 30 Phenelzine: 38, 34 Placebo: 34, 28
Zanarini et al[54] 2004	Borderline personality disorder, female outpatients	NAR	Active drug or alcohol abuse, psychotropic use, suicidal, medically ill, seizures, depression	8	Olanzapine: 16, 16 Fluoxetine: 14, 13 Olanzapine/fluoxetine: 15, 13

[a]Aggression before trial: minimal required frequency and/or severity for study inclusion.
[b]Duration of the trial treatment phase.
[c]First number represents the number of participants at the beginning of the study; second number indicates the number of participants minus dropouts.
[d]The Others category represents studies comparing active drugs of 2 different classes.
Abbreviations: NAR = no aggression before baseline required for study inclusion, OAS-M = Overt Aggression Scale-Modified, PANSS = Positive and Negative Syndrome Scale, PTSD = posttraumatic stress disorder.
Symbol: ? = number not stated.

Table 2. Study Outcomes

Study	Measures	Side Effects	Jadad Score[a]	Generalizability[b]	Outcome[c]
Antipsychotic agents					
Blin et al[59] 1996	PAS	No serious side effects. More extrapyramidal symptoms in haloperidol group, except hypokinesia and bradykinesia, which were higher for the risperidone group	3	1	NS
Citrome et al[34] 2001	PANSS hostility	7 patients with hematologic problems and seizures (unclear which arm)	4	1	Clozapine SS to risperidone and haloperidol, but not to olanzapine. Improvement for clozapine, but not for other drugs, was independent from overall antipsychotic effect
Czobor et al[28] 1995	PANSS hostility	Not mentioned	2	1	Risperidone SS superior to haloperidol and placebo. Haloperidol not SS as compared to placebo
Marder et al[61] 1997	PANSS hostility-excitement cluster	Not mentioned	3	1	Risperidone SS superior to haloperidol and placebo
Min et al[27] 1993	PANSS hostility	No between-group differences; no serious side effects	4	1	NS
Monnelly et al[45] 2003	OAS (modified for outpatients), STAS-S, STAS-T, and Buss-Durkee	Mild side effects in both groups	3	0	NS
Peuskens[60] 1995	PANSS hostility	More extrapyramidal symptoms for haloperidol; increase of weight for risperidone	4	1	SS
Zanarini and Frankenburg[53] 2001	SCL-90	In the olanzapine group, 1 patient with extrapyramidal symptoms, and, in the whole group, weight gain	5	0	SS
β-Adrenergic–blocking drugs					
Allan et al[30] 1996	BPRS hostility factor	1 dropout in both groups due to blood pressure drops	3	1	NS
Alpert et al[31] 1990	OAS	1 dropout in both groups due to blood pressure drops	3	1	Not presented
Caspi et al[32] 2001	OAS	3 dropouts due to adverse events: bronchitis, bronchospasm, syncope	3	1	SS (frequency and severity)
Maoz et al[42] 2000	OAS, CGI-S, STPI anger state, STPI anger trait, MAI	Less extrapyramidal symptoms in the propranolol group	4	0	SS for STPI anger state and trait, not for other outcomes
Ratey et al[47] 1992	OAS, BPRS hostility-suspicion	4 dropouts due to adverse events: low blood pressure, syncope, bronchospasm	4	1	SS for OAS
Anticonvulsants					
Citrome et al[33] 2004	PANSS hostility	No serious side effects; no between-group differences	3	1	SS better results at days 3 and 7—but **not** at endpoint
de la Fuente and Lotstra[37] 1994	SCL-90	Not mentioned	3	0	NS
Frankenburg and Zanarini[40] 2002	SCL-90 anger-hostility, OAS (McLean version)	Low rate of adverse events in both groups	5	0	SS on both scales
Hollander et al[56] 2003	OAS (modified for outpatients)	Mild to moderate in severity; 21 (active drug) vs 4 (placebo) dropouts due to adverse events	3	1	SS
Hollander et al[55] 2001	OAS (modified for outpatients), AQ	Not mentioned	3	0	NS improvement
Nickel et al[46] 2005	STAXI (5 different anger subscales)	Weight reduction; no severe adverse effects	3	0	SS improvement on 4 of the 5 subscales

continued

Table 2. Study Outcomes (cont.)

Study	Measures	Side Effects	Jadad Score[a]	Generalizability[b]	Outcome[c]
Antidepressants					
Coccaro and Kavoussi[57] 1997	OAS (modified for outpatients), AQ, CGI-I	Mild-moderate; 1 dropout due to adverse events	3	1	SS from week 10 till endpoint
Davidson et al[36] 1981	SCL-90 anger scale	Not mentioned	5	0	Imipramine SS to phenelzine
Davidson et al[35] 2002	DTS anger irritability subscale	Not mentioned	4	0	SS
McDougle et al[44] 1996	Brown Aggression Scale[71]	No medically significant side effects	4	1	SS from week 4 till endpoint
Fava et al[39] 1997	AAQ	Not mentioned	2	1	NS
Fassino et al[38] 2002	STAXI Trait Anger scale	Not mentioned	2	0	SS
van der Kolk et al[58] 1994	Buss-Durkee	Diarrhea, sweating, and headaches more frequently in fluoxetine group	3	1	NS
Rinne et al[48] 2002	BPDSI anger subscale	More nausea in fluvoxamine group	3	0	NS
Salzman et al[49] 1995	POMS, OAS (McLean version)	Not mentioned	4	0	POMS: SS; OAS-R: NS
Vartiainen et al[52] 1995	SDAS, CGI-S, SOAS	No significant differences between active drug and placebo	3	1	SS: frequency SOAS
Others[d]					
Dorrego et al[29] 2002	OAS	Methylphenidate: nausea, weight loss; lithium: motor slowness	4	1	Same effect in both arms
Lipman et al[41] 1986	SCL-80	Chlordiazepoxide: drowsiness; imipramine: higher pulse rate and blood pressure	4	0	No improvement from baseline for imipramine; for chlordiazepoxide, deterioration from baseline
Mattes[43] 1990	Global improvement rating scale	Not mentioned	2	1	No difference between carbamazepine and propranolol
Soloff et al[51] 1989	SCL-90, IMPS hostile belligerence, Buss-Durkee	Not mentioned	4	1	Haloperidol SS improvement compared to amitriptyline and placebo on the SCL-90, but not on the other measures. Amitriptyline SS only on Buss-Durkee compared to placebo
Soloff et al[50] 1993	Buss-Durkee, SCL-90, IMPS hostility	Not mentioned	3	0	Haloperidol SS improvement compared to phenelzine and placebo on the IMPS (not on other scales)
Zanarini et al[54] 2004	OAS (modified for outpatients)	More sedation and weight gain in the olanzapine monotherapy group	3	0	Olanzapine as efficacious as olanzapine/fluoxetine in reducing aggression

[a]Jadad score ≥ 3 = acceptable methodological quality.
[b]0 = poor generalizability; 1 = acceptable generalizability.
[c]SS = statistically significant in favor of the active drug compared to placebo unless otherwise specified; NS = not significant.
[d]The Others category represents studies comparing active drugs of 2 different classes.
Abbreviations for outcome measures and associated references: AAQ = Anger Attacks Questionnaire,[67] AQ = Aggression Questionnaire,[68] BPDSI = Borderline Personality Disorder Severity Index,[64] BPRS = Brief Psychiatric Rating Scale,[70] Buss-Durkee = Buss-Durkee Hostility Inventory,[69] CGI-I = Clinical Global Impressions of Improvement scale,[72] CGI-S = Clinical Global Impressions-Severity of Illness scale,[72] DTS = Davidson Trauma Scale,[73] IMPS = Inpatient Multidimensional Psychiatric Scale,[75] MAI = Multidimensional Anger Inventory,[76] OAS = Overt Aggression Scale,[62,77,83] PANSS = Positive and Negative Syndrome Scale,[63] PAS = Psychotic Anxiety Scale,[78] POMS = Profile of Mood States,[79] SCL-80 = Hopkins Symptom Checklist-80,[74] SCL-90 = Hopkins Symptom Checklist-90,[74] SDAS = Social Dysfunction and Aggression Scale,[66] SOAS = Staff Observation Aggression Scale,[65] STAS-S = Spielberger State-Trait Anger Scale-State version,[82] STAS-T = Spielberger State-Trait Anger Scale-Trait version,[82] STAXI = State-Trait Anger Expression Inventory,[80] STPI = State-Trait Personality Inventory.[81]

Table 3. Evidence Synthesis

Drug	Qualitative Evidence Synthesis: N	No. of Studies	Proportion of Statistically Significant Studies	Obtained Evidence	Proportion of Studies With Acceptable Generalizability
Classical antipsychotics vs placebo	308	3	2/3	Weak evidence of efficacy	1/2
Atypical antipsychotics vs placebo and/or haloperidol	2122	7	3/7	Weak evidence of efficacy compared to placebo and haloperidol	5/7
β-Adrenergic blockers vs placebo	169	5	3/5	Weak evidence of efficacy	4/5
Anticonvulsants vs placebo	450	6	3/6	Weak evidence of efficacy	2/6
Antidepressants vs placebo	1024	10	6/10	Weak evidence of efficacy	6/10

data, which were not available directly from the studies. Consequently, we could only perform a qualitative evidence synthesis.

Antipsychotic agents. Two 3-armed RCTs[50,51] performed by the same research group in a borderline personality disordered population comparing haloperidol and an antidepressant to placebo were found. In both studies,[50,51] haloperidol was found to be statistically significantly superior to placebo on the Hopkins Symptom Checklist-90 (SCL-90)[74] but not on the Inpatient Multidimensional Psychiatric Scale (IMPS)[75] hostility items. In one 3-armed RCT[61] comparing risperidone to haloperidol and placebo in a schizophrenic population, no benefit for haloperidol as compared to placebo was found.

Seven studies with acceptable methodological quality comparing atypical antipsychotics to haloperidol and/or placebo in subjects with schizophrenia,[27,34,59–61] borderline personality disorder,[53] or posttraumatic stress disorder[45] were evaluated. In 2 large-scale studies, risperidone was superior to haloperidol[60,61] and placebo[61] on the PANSS hostility factor in dosages of more than 2 mg daily. In 4 studies[27,34,45,59] comparing risperidone to haloperidol or placebo, no benefit for risperidone was reported. However, in 3 of these studies[27,45,59] sample size was small, and in one study only a 0.5-mg daily dose of risperidone was used.[45] One study[34] showed clozapine to be significantly superior to haloperidol, risperidone, and olanzapine in reducing hostility apart from the overall antipsychotic effect in a schizophrenic population resistant to previous neuroleptic treatment. The antiaggressive mechanism of clozapine in that study appeared unrelated to overall psychopathological improvement. One study[53] showed olanzapine to be superior to placebo in borderline personality disordered outpatients.

Overall, we conclude that there is weak evidence of efficacy for antipsychotic agents in treatment of aggression. Furthermore, weak evidence was found for the superiority of atypical antipsychotics over typical antipsychotics.

β-Adrenergic blockers. β-Adrenergic blockers are effective in decreasing aggression in organic brain diseases.[86] For the general adult psychiatric population, we found 5 studies,[30–32,42,47] all conducted in a schizophrenic population. In 3 studies using the β-adrenergic blocker pindolol,[32] propanolol,[42] or nadolol[47] and conducted in a chronic schizophrenic population, a significant reduction of aggression was found with β-adrenergic blockers as compared to placebo. Two[32.47] of these 3 studies were conducted in a chronic schizophrenia population. The 2 studies[30,31] not showing positive results in favor of the β-blockers were conducted in a population consisting of schizophrenic patients with an acute exacerbation. Thus, according to our decision rules, there is weak evidence for the antiaggressive properties of β-adrenergic–blocking drugs in schizophrenic patients. However, it is unclear whether these benefits outweigh the observed adverse events like syncopes and bronchospasms.

Anticonvulsants. Four studies were retrieved assessing antiaggressive properties of valproate (divalproex sodium), compared to placebo.[33,40,55,56] Furthermore, in one study, topiramate was used as active drug,[46] and, in another study, carbamazepine was used.[37] In 3 of the 6 studies,[40,46,56] anticonvulsants were superior to placebo. The patient populations in these 3 studies consisted of cluster B personality disordered outpatients. In the 3 studies not favoring anticonvulsants over placebo, either the sample size was low[37,55] or the population consisted of patients with an acute exacerbation of mental illness,[33] which suggests that the statistical power was low.

With 3 of the 6 studies favoring anticonvulsants to placebo, we concluded that there is weak evidence of efficacy in the management of aggression with anticonvulsants in cluster B personality disordered outpatients. No serious adverse events were observed or mentioned in the different studies.

Antidepressants. Ten studies with acceptable methodological quality comparing antidepressants to placebo were evaluated.[35,41,44,48–52,57,58] Of the 10 available studies, 6 studies (fluoxetine,[57] fluvoxamine,[44] sertraline,[35] amitriptyline,[51] imipramine,[36] and citalopram[52]) with clinical heterogeneity across studies (autism,[44] PTSD,[35] schizophrenia,[52] depression,[36] and cluster B personality disorder[51,57]) showed a significant improvement for the active drug group compared to the placebo group. The total study follow-up of 4 of 6 studies with positive results was 12 or 13 weeks,[35,44,52,57] while, in 4 studies not favoring antidepressant to placebo,[41,48,50,58] the study duration

was less than 12 weeks (a range from 5 to 8 weeks). Additionally, in 2 of 6 studies with positive results,[52,57] patients were required to have a certain baseline level of aggression compared to none of the 5 studies not showing positive results. Furthermore, in 1 study[36] comparing imipramine to phenelzine, superiority of imipramine was observed. We conclude that there is weak evidence of efficacy for the use of antidepressants for the management of aggression across a diversity of diagnoses.

Comparison of different drug classes. We found 4 studies[29,41,43,54] that could not be classified into subgroups because drugs belonging to 2 different therapeutic drug classes were compared to each other (carbamazepine vs. propranolol,[43] lithium vs. methylphenidate,[29] the combination of olanzapine and fluoxetine vs. monotherapy,[54] and imipramine vs. chlordiazepoxide[41]). One of those studies,[43] which compared carbamazepine to propranolol, had poor internal validity as reflected by a Jadad score of less than 3 and, therefore, was not evaluated for evidence synthesis. In the other 3 studies,[29,41,54] efficacy is suggested for both the combination therapy of olanzapine and fluoxetine and monotherapy of olanzapine compared to monotherapy of fluoxetine[54] and imipramine compared to chlordiazepoxide,[41] and no differences between lithium and methylphenidate were observed.

DISCUSSION

Although aggressive patients use more psychotropics as compared to nonaggressive patients, no strong evidence of efficacy was found for any of the drug classes. Weak evidence of efficacy was found for antipsychotics, antidepressants, anticonvulsants, and β-adrenergic–blocking drugs. Atypical antipsychotics were found to be superior to typical antipsychotic agents. Several methodological and generalizability issues complicated the evidence synthesis.

Methodological Limitations

In most studies evaluated, the follow-up period was 6 to 12 weeks, but 9 studies had less than 6 weeks of follow-up.

Although 3- to 6-week trials can, in some cases, be considered adequate, for instance in the case of antipsychotics,[87] longer follow-up seems more appropriate when studying the effects of the treatment of aggression. Firstly, longer follow-up might be required to reach optimal drug efficacy, and, secondly, changes in aggressive behavior are usually measured more reliably in a longer follow-up period when incident-based instruments or self-report questionnaires are used to measure changes in aggressive behavior. Incident-based measurement scales, like the OAS[62] and the Staff Observation Aggression Scale (SOAS),[65] are designed to detect changes in aggressive behavior by measuring the frequency and the severity of observed aggressive incidents. Especially when the baseline frequency of aggressive behavior is low, longer follow-up is required to be able to detect changes in aggressive behavior reliably. In addition, when self-report questionnaires are used to measure changes in aggressive behavior, a potential lag time between the patients' self-recognition that aggressive behavior has diminished in frequency and severity and self-perception that one is still capable of engaging in aggressive acts warrants a longer prospective window of patient assessment.[57]

Different limitations influenced the statistical power of the studies. When study power is low, insufficient evidence of efficacy does not automatically implicate evidence of no efficacy. We identified the following 4 factors that may have led to a lack of power in individual studies to show evidence of efficacy of one drug above another. Firstly, study samples tended to be small. Secondly, because we expected few trials to investigate drug effects as primary outcome, we also included RCTs investigating drug effects on aggression or aggression-related symptoms as a secondary outcome. However, as the studies with aggression or aggression-related symptoms as a secondary outcome are not primarily designed to detect reduction in aggressive behavior, they might lack power to show evidence of efficacy. The third factor that might have led to a reduction of statistical power was the low baseline aggression in several studies. The use of a minimum baseline aggression level as an inclusion criterion can avoid this problem. A fourth factor that might have lowered the statistical power is the use of an inadequate source population. In some of the studies, the study population consisted of schizophrenic patients experiencing an acute exacerbation.[30,31,33,42] Acute psychiatric illness is associated with aggression; however, once stabilized, aggression does not necessarily remain an ongoing problem.

To avert the problem of low statistical power, we intended to meta-analyze the study results. For meta-analysis, calculation of effect sizes is required. As numerous continuous scales were used in the individual studies, study outcomes were not directly comparable. In such cases, the computation of standardized effect sizes, i.e., SMD, is required. Unfortunately, either many studies did not provide the data required to calculate this effect size, or the reliability of such data was considered doubtful. We, therefore, had to rely on qualitative evidence synthesis instead of quantitative data synthesis.

The impossibility of calculating effect sizes not only precluded quantitative evidence synthesis, but also hampered our qualitative evidence synthesis, while studies were defined as positive if the study results were statistically significant or clinically relevant. Clinical relevance was defined as an effect size of 0.5 or more. This implies that some studies, especially those with low statistical power, might have been incorrectly classified as not positive.

Generalizability to Daily Clinical Practice

In this review, an attempt was made to assess the generalizability of the included studies to daily clinical practice. Poor generalizability to patients seen in daily practice is one of the limitations particularly associated with RCTs.[88–90] Previous studies showed that patients with comorbid disorders are often excluded from trials.[19,89] We have indications that the aggressive patient commonly seen in daily clinical practice was excluded from the evaluated trials because of the recruitment procedures depending on voluntary participation, the strict inclusion and exclusion criteria, and the sometimes inadequate resource population.

Recommendations for Further Research

As only weak evidence of efficacy was found, further research in this field is required. For future research, consensus on the use of aggression measurement scales should be reached, which might facilitate the conduct of meta-analytic pooling. The assessment of changes in aggressive behavior should be done with observer-rated scales. We suggest using both an incident-based scale, like the OAS[62] or SOAS,[65] and a scale measuring behavioral and psychopathologic changes, like the SDAS.[66]

Furthermore, the results of future trials should be more generalizable to daily clinical practice. More generalizable results can be achieved by conducting pragmatic trials.[19,90] Pharmacoepidemiologic research might be another option to obtain evidence generalizable to daily clinical practice.[88]

Drug names: carbamazepine (Carbatrol, Equetro, and others), chlordiazepoxide (Librium and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lithium (Lithobid, Eskalith, and others), methylphenidate (Ritalin, Metadate, and others), nadolol (Corgard and others), olanzapine (Zyprexa), olanzapine and fluoxetine (Symbyax), phenelzine (Nardil), pindolol (Visken and others), propranolol (Innopran, Inderal, and others), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax).

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