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Trials Assessing Pharmacotherapeutic Management of Aggression in Psychiatric Patients: Comparability with Clinical Practice

Introduction

Aggression is an important issue in mental health departments, as it negatively influences the well-being of both patients and staff workers and results in high costs [4, 21]. Pharmacotherapy is one of the tools used to prevent or reduce aggressive behaviour and incidents. Our group has shown that only weak empirical evidence is available for the effectiveness of pharmacotherapeutic management of aggression [18]. This systematic review was restricted to randomized controlled trials (RCTs) as these are considered to be the gold standard to obtain the most valid evidence for the effect of interventions [38]. However, one of the observations from the review was that characteristic aggressive patients seen in clinical practice may be different from those included in RCTs, because of recruitment procedures depending on voluntary participation, strict inclusion and exclusion criteria, and sometimes small populations. This selection process may hamper the comparability of RCT populations to daily clinical practice patients, as has been shown by others, especially in psychiatric populations. Zimmerman [44], for example, showed that only 14% of depressed patients seen in daily practice would qualify for trial participation when applying exclusion criteria that are commonly used in RCTs. Another recent study showed that in patients suffering from epilepsy, less than thirty percent would qualify to participate in a typical randomized controlled trial based on the most frequently applied exclusion criteria.

Discussion

The low comparability of patients included in RCTs with those seen in clinical practice may decrease the generalizability of the findings from RCTs to clinical practice.

Methods

Exclusion criteria that were used in at least 20% of the RCTs were applied to a sample of aggressive inpatients from clinical practice, in order to find what proportion of these patients would be eligible to participate in the reviewed, high quality RCTs.

Results

Only 30% of aggressive psychiatric patients as seen in clinical practice would be eligible to participate in a typical randomized controlled trial based on the most frequently applied exclusion criteria.

Discussion

The low comparability of patients included in RCTs with those seen in clinical practice may decrease the generalizability of the findings from RCTs to clinical practice.
Subsequently, these criteria were applied to the sample of aggressive incidents during the study period, as recorded with observation aggression scale-revised (SOAS-R) [31]. Patients eligible for our study populations had all had aggression in adult (18–65 years old) psychiatric patients in general psychiatric settings. This means that RCTs applying to specialized psychiatric settings – like child psychiatry, mental retardation, and organic brain diseases – or to non-psychiatric settings – like prisons – were not included in this review. For this review, only those RCTs of sufficient methodological quality, which was defined as a Jadad score [22] of three or more, were selected for the present study.

The population sampled from clinical practice consisted of all patients of three long-stay wards of Altrecht Mental Health Care Institute who engaged in aggressive behaviour during admission. The three participating wards were units for forensic psychiatry, a centre for intellectually disabled adolescents and adults with severe disruptive behaviour, and a ward for juveniles with externalizing behaviour disorders. Aggressive behaviour on these wards was continuously monitored and recorded by the staff using the staff observation aggression scale-revised (SOAS-R) [31]. Patients eligible for our study populations had all had been admitted for at least two weeks during the period September 2004 until December 2005. Patients with one or more aggressive incidents during the study period, as recorded with the SOAS-R, were selected.

For consenting patients, physical examination, medical history and laboratory values were determined during the first week of admission. These data as well as demographic information were extracted from the hospital records. The study protocol was approved by the Institutional Review Board of the hospital.

Data analysis
All selected RCTs were reviewed and all exclusion criteria that were used in at least six (20 %) of the 31 RCTs were selected. Subsequently, these criteria were applied to the sample of aggressive inpatients from clinical practice, in order to calculate what proportion of these patients would be eligible to participate in the reviewed, high quality RCTs. Lastly, characteristics of eligible patients were compared with characteristics of ineligible patients.

As the patients from clinical practice were all inpatients, a sub-analysis, with the use of only the exclusion criteria used in at least 20 % of the RCTs conducted in inpatient settings, was performed.

Results

RCTs
The RCTs were conducted in the following patient groups: schizophrenic patients (N = 12 [39 % of the RCTs]) and patients with cluster B personality disorder (N = 12 [39 % of the RCTs]), patient suffering from PTSD (N = 3 [10 % of the RCTs]), depressive disorder (N = 2 [7 % of the RCTs]), ADHD (N = 1 [3 % of the RCTs]) and autistic disorder (N = 1 [3 % of the RCTs]). The exclusion criteria extracted from the RCTs are presented in Table 1.

A number of exclusion criteria, including “relevant somatic disorder”, “physical disorder”, “unstable medical disease” and “abnormal routine lab”, were generally not well-defined. The authors of studies in which these exclusion criteria were not well-defined, were contacted by e-mail for further specification of these criteria. Response rate was low (3 out of 15 = 20 %). On basis of the responses and the other reviewed RCTs in which somatic illnesses or deviant laboratory values as exclusion criteria were defined more precisely, we decided to further specify the criteria as follows: “relevant somatic disorder”, “physical disorder” and “unstable medical disease” included neurological diseases, COPD and asthma, cardiovascular disease, liver disease and renal failure, whereas “abnormal routine lab” comprised deviant laboratory tests findings, including liver function, kidney function, thyroid function and haemogramme. The exclusion criterion “the use of psychotropics other than the study medication” was used in 58 % of the trials with borderline

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>Percentage of all trials in which the criterion was used</th>
<th>Percentage of trials, conducted in inpatient setting, in which the criterion was used</th>
</tr>
</thead>
<tbody>
<tr>
<td>substance abuse (alcohol or drugs)</td>
<td>54.8</td>
<td>44.4</td>
</tr>
<tr>
<td>abnormal routine laboratory values</td>
<td>51.6</td>
<td>66.7</td>
</tr>
<tr>
<td>clinically relevant systemic somatic disorder (heart, renal, hepatic, neurological, asthma and COPD)</td>
<td>51.6</td>
<td>61.1</td>
</tr>
<tr>
<td>pregnancy</td>
<td>38.7</td>
<td>33.3</td>
</tr>
<tr>
<td>use of other psychotropics than the study drug</td>
<td>35.5</td>
<td>16.7</td>
</tr>
<tr>
<td>lactating</td>
<td>32.2</td>
<td>27.8</td>
</tr>
<tr>
<td>suicidal ideation</td>
<td>19.3</td>
<td>0.0</td>
</tr>
<tr>
<td>without contraception</td>
<td>16.1</td>
<td>11.1</td>
</tr>
<tr>
<td>unstable medical disorder</td>
<td>16.1</td>
<td>16.7</td>
</tr>
<tr>
<td>organic brain disorder</td>
<td>9.7</td>
<td>38.9</td>
</tr>
<tr>
<td>psychotherapy</td>
<td>9.7</td>
<td>0.0</td>
</tr>
<tr>
<td>depot neurolepticum</td>
<td>9.7</td>
<td>16.7</td>
</tr>
<tr>
<td>women</td>
<td>6.4</td>
<td>0.0</td>
</tr>
<tr>
<td>men</td>
<td>3.2</td>
<td>0.0</td>
</tr>
<tr>
<td>history of psychiatric hospitalization</td>
<td>3.2</td>
<td>0.0</td>
</tr>
<tr>
<td>IQ &lt; 75</td>
<td>3.2</td>
<td>5.6</td>
</tr>
<tr>
<td>drug-induced psychosis</td>
<td>3.2</td>
<td>5.6</td>
</tr>
<tr>
<td>self-mutilation</td>
<td>3.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>
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patients, but in none of the trials conducted in a study population consisting of schizophrenic patients.

Clinical practice sample
The clinical practice sample consisted of 106 aggressive patients. Patients’ characteristics are displayed in Table 2. Exclusion criteria were applied in descending order of appearance in the trials. Current drugs and/or alcohol abuse was observed in 29% of the patients. Fourteen patients (13%) had a relevant somatic disorder. Furthermore, three patients (3%) refused to undergo a physical examination, which would be reason for exclusion in an RCT. Abnormal routine lab was observed in 13% of the patients, whereas 5% of the patients refused to give a blood sample. No patients were pregnant or lactating. Finally, in several studies patients were excluded if other psychotropics were used concomitantly with the study drug. We assumed that patients from our study sample using two or more psychotropics would not likely be switched to only one study-drug. Therefore, from our study sample patients using more than one psychotropic, i.e., almost one third (34%), were considered ineligible for a trial. With the application of these criteria on the study population, only 30% of the patients would be eligible for trial participation (Fig. 1). As use of other psychotropics was not a frequently used exclusion criterion in the RCTs conducted in patients with schizophrenia, we also calculated the percentage of eligible schizophrenic patients, without application of this criterion, which resulted in a percentage of 43% of patients that would be eligible. Lastly, in the subanalysis in which only exclusion criteria of the RCTs conducted in inpatients setting were applied to the clinical practice sample, 46% of patients appeared to be eligible.

Eligible versus ineligible patients
The eligible patients were compared with the ineligible patients, results of this comparison are shown in Table 3. Eligible patients were significantly younger and were less frequently diagnosed with a personality disorder. Concerning the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with aggressive incident(s) (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (mean, SD)</td>
<td>27.3 (10.4)</td>
</tr>
<tr>
<td>aggressive incidents per month (mean, SD)</td>
<td>1.9 (4.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>male sex</td>
<td>76 (71.7)</td>
</tr>
</tbody>
</table>

diagnosis (DSM IV)
– Axis I
– psychotic disorder | 49 (46.2) |
– mood disorder | 11 (10.4) |
– anxiety | 6 (8.8) |
– alcohol dependence/abuse | 9 (8.5) |
– drug dependence/abuse | 27 (25.5) |
– pervasive disorder | 10 (9.4) |
– ADHD & disruptive behaviour | 24 (22.6) |
– other | 11 (10.4) |
– Axis II
– personality disorder | 14 (13.2) |
– mental retardation | 40 (37.7) |
regular medication use
– antidepressants | 18 (17.0) |
– antipsychotics | 54 (50.9) |
– benzodiazepines | 33 (31.1) |
– mood stabilizer | 11 (10.4) |
– somatic medication | 33 (31.1) |

Table 2 Clinical practice sample.
frequency and severity of aggression, no differences were observed between eligible and ineligible patients.

**Discussion**

The current results suggest that, based upon the most frequently applied exclusion criteria, only 30% of aggressive psychiatric patients as seen in clinical practice would be eligible to participate in a typical randomized controlled trial investigating the pharmacological maintenance treatment of aggression. This finding is in line with the proportions reported in two previous studies, in which 14% and 30% of patients from clinical practice were found to be eligible for trial participation in a clinical practice population treated for depression and epilepsy, respectively [39, 44].

These findings warrant the conclusion that the evidence for the pharmacological management of aggression not only appears to be weak [18] but that, additionally, the patients in trials are different from the patients of clinical practice, or at least different from typical psychiatric long-stay inpatients. Subsequently this raises the question whether the trial outcomes are generalizable to clinical practice. It is quite well imaginable that they are not. For example, it is likely that more somatic comorbidity influences the generalizability of trials, e.g., due to the use of co-medication. Furthermore, comparison of the group of the eligible with the non-eligible patients shows that the eligible patients differ from the non-eligible patients, at least for diagnosis and age.

In addition to the exclusion criteria applied, other characteristics of the evaluated RCTs are likely to decrease the comparability of trials to clinical practice. Firstly, previous research suggests that aggressive patients are less likely to give informed consent [14]. This might lead to an underrepresentation of severely aggressive patients. Furthermore, the setting of many RCTs (~40% in outpatient departments) and the recruitment methods (e.g., advertisement) might also have contributed to an underrepresentation of severely aggressive patients in the RCTs. It is well imaginable that the aetiology of aggression of severely aggressive patients differs from the aetiology in mildly aggressive patients, thereby requiring different pharmacotherapeutic strategies.

In conclusion, it is likely that the low comparability of the patients in RCTs with the patients from practice affects the generalizability of the efficacy of trial medication and observed side effects. However, with the available data we were not able to investigate this. To investigate this, other research, such as conducted by Wisniewski et al. [45], is needed. In that study the researchers showed that depressive patients who would be ineligible for a phase III trial with antidepressants, experienced more severe side effects and had lower remission and response rates compared to the eligible patients.

From a clinical point of view we therefore conclude that it might be understandable that with only weak evidence for efficacy, psychotropics are used (off-label) in an attempt to manage such a difficult behaviour as aggression. However, from our point of view, prescribers should be well aware of the limited available evidence with a probable low generalizability to clinical practice, and certainly stop the medication if no effect is observed. This study has some limitations. The criterion “multiple psychotropic use” was observed in the trials conducted in populations consisting of patients with cluster B personality disorder, but not in the trials conducted in populations consisting of schizophrenic patients. The percentage of patients that could be included in a study would increase to 46% if multiple psychotropic use would be allowed. This suggests that an analysis, stratified for diagnosis would be more appropriate. However, the number of included trials was not enough to conduct such an analysis.

Furthermore, because the methodology of the trials was not always clearly described, we may have interpreted the criteria concerning somatic disorders and abnormal routine laboratory values not strictly enough or too strictly when cut-off points were not mentioned in the RCTs. Future studies possibly could give more insight, with the current regulations binding researchers to publish their study protocols in an internet database.

**Conclusion**

With an eligibility percentage of 30–46%, we conclude that the patient comparability of trials, investigating the pharmacological management of aggression, to clinical practice is low. Furthermore, other RCT characteristics suggest that patients displaying severe aggression are not eligible in RCTs. The low comparability may decrease the generalizability of RCT findings to clinical practice.

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**Table 3** Comparison of eligible and ineligible patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included patients</th>
<th>Excluded patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>age (mean, SD)</td>
<td>23.5 (9.9)</td>
<td>28.9 (10.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>aggressive incidents per 100 days (median)</td>
<td>4.2</td>
<td>2.5</td>
<td>0.19</td>
</tr>
<tr>
<td>severely aggressive</td>
<td>28 (87.5)</td>
<td>55 (74.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>male sex</td>
<td>20 (62.5)</td>
<td>56 (75.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>diagnosis (DSM IV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– axis I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– psychotic disorder</td>
<td>11 (34.4)</td>
<td>38 (51.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>– mood disorder</td>
<td>4 (12.5)</td>
<td>7 (9.5)</td>
<td>0.64</td>
</tr>
<tr>
<td>– pervasive disorder</td>
<td>6 (18.8)</td>
<td>4 (5.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>– ADHD &amp; disruptive behaviour</td>
<td>11 (34.4)</td>
<td>13 (17.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>– axis II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– personality disorder</td>
<td>2 (6.2)</td>
<td>17 (23)</td>
<td>0.04</td>
</tr>
<tr>
<td>– mental retardation</td>
<td>10 (31.2)</td>
<td>30 (40.5)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

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Acknowledgements

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Affiliations
1 Altrecht Institute for Mental Health Care, Den Dolder, The Netherlands
2 Department of Pharmacoeconomics and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht, The Netherlands
3 Arkin Institute for Mental Health Care, Amsterdam, the Netherlands
4 Academic Center of Social Sciences, Radboud University Nijmegen, The Netherlands
5 Department of Clinical Pharmacy, Division Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands

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