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Research report

Pharmacological treatment of acute mania in psychiatric in-patients between 1994 and 2004

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Abstract

Background: In a cross-section approach we investigated prescription practice in acute mania in 63 German, Swiss and Austrian hospitals between 1994 and 2004.
Methods: Our data were gathered from a large drug safety program (AMSP) within which on two reference days each year all administered drugs are recorded. For the present study, all cases with a primary diagnosis of acute euphoric mania ($n=1291$) or mixed-state mania ($n=143$) were identified. Prescription rates from two periods, 1994 to 1999 and 2000 to 2004, were compared.
Results: In euphoric mania, prescription of lithium decreased by about one-fifth (43.3% to 34.5%, $p<0.01$), while prescription of anticonvulsants increased by one-half (from 40.0% to 60.7%, $p<0.001$). Administration of atypical antipsychotics more than doubled (18.5% to 43.9%, $p<0.001$), while use of typical antipsychotics decreased significantly (56.9% to 27.8%, $p<0.001$). Overall prescription rates of antipsychotics (79.6% vs. 81.6%) and antidepressants (14.0% vs. 15.5%) remained stable, while administration of tranquilizers increased significantly (26.3% to 34.3%, $p<0.01$).

In mixed-state mania, similar trends over time to those seen in euphoric mania were observed for lithium (43.2% to 33.3%), anticonvulsants (50.0% to 69.7%, $p<0.05$) and tranquilizers (22.7% to 40.4%). Prescription rates of antipsychotics slightly increased (63.6% to 72.7%), while prescription of antidepressants slightly decreased (54.5% to 46.5%).

Polypharmacy was a common phenomenon: patients with euphoric mania were treated with a mean number of 2.9 ± 1.2 psychotropic agents, and patients with mixed-state mania with 3.3 ± 1.5 psychotropic agents. Both groups showed a significant increase over time.

Second-generation atypical antipsychotics were adopted quite rapidly for the treatment of acute mania considering the availability of the scientific evidence at that time. Off-label use was a common phenomenon. Deviations from recommended guidelines were found mainly in the use of antidepressant and antipsychotic drugs both in mixed-state and euphoric mania.
Conclusions: Naturalistic prescription studies like this may encourage a critical scrutiny of clinical treatment habits and may also drive further research thus moderating potential differences between evidence-based knowledge and everyday clinical practice.

Keywords: Mania; Prescription; Anticonvulsants; Lithium; Antipsychotics; Antidepressants

1. Introduction

Pharmacological treatment of acute mania has been characterized by an expanding pharmacopoeia over the

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past decade. Fifteen years ago, lithium was the only approved drug for the treatment of mania. Since then various agents have been introduced. Valproate is a proven alternative to lithium (Pope et al., 1991; Freeman et al., 1992; Bowden et al., 1994). Other anticonvulsants considered for the treatment of mania have been carbamazepine (Brown et al., 1989; Small et al., 1991), oxcarbazepine (Hummel et al., 2002), lamotrigine (Ichim et al., 2000) and topiramate (Marcotte, 1998). The late 1990s also saw the emergence of the second-generation atypical antipsychotics olanzapine, risperidone and quetiapine, originally developed for treatment of schizophrenia, but soon considered and tested as possible mood stabilizing agents (Berk et al., 1999; Tohen et al., 1999; Segal et al., 1998; Ghaemi and Katzow, 1999).

The broad research on the usefulness of these various substances did not clarify the picture. On the contrary, "bipolar disorder presents a challenge for even the most experienced clinicians" (Sachs, 2003, p. 35). The efficacy of a certain mood stabilizer in one manifestation of mania does not necessarily mean that this drug is also the treatment of choice in another variant. To give clinical practitioners some orientation in this difficult terrain, several evidence-based guidelines and decision algorithms have been developed. Among others, practice guidelines have been drawn up by the American Psychiatric Association (1994, 2002), the Department of Veterans Affairs (Bauer et al., 1999), the Texas Medication Algorithm Project (Suppes et al., 2001), the World Federation of Societies of Biological Psychiatry (Grunze et al., 2003) and the British Association for Psychopharmacology (Goodwin, 2003).

However, questions remain as to what extent treatment guidelines affect the clinician's actual practice. Individual experience, tradition and training may hinder the acceptance of the available scientific evidence. On the other hand, guidelines elaborated from double-blind placebo-controlled clinical trials or double-blind comparator studies do not necessarily truly reflect clinical situations and requirements. Expert consensus guidelines based on the subjective ratings of their panel members (Frances et al., 1996; Sachs et al., 2000) tried to overcome the limitations inherent in conventional guidelines, but it could be argued that they do not meet the terms of evidence-based medicine.

With the present study we intend to promote discussion on this topic. Using a naturalistic cross-section approach, we investigated the pharmacological treatment of acute mania from 1994 to 2004 in 63 German, Swiss and Austrian hospitals. Special emphasis was placed on the various established and putative mood stabilizing agents: Anticonvulsants like carbamazepine, valproate or lamotrigine as well as the newer atpypical antipsychotics like olanzapine, risperidone or quetiapine. Our purpose was to analyze prescription practice and its change over time as well as to compare our results with both guideline recommendations and scientific evidence at the given time.

2. Methods

The data for the present investigation were gathered from the AMSP database (Grohmann et al., 2004). The AMSP (*A*rznei*m*ittel*s*icherheit in der *P*sychiatrie) is a drug safety program for the continuous registration of adverse side effects in psychiatric in-patients. It was initiated at the Psychiatric University Hospital in Munich in 1990. By 1994, the AMSP program comprised four psychiatric university hospitals, four psychiatric state hospitals and one psychiatric department of a municipal hospital. By 2004, 45 psychiatric institutions in Germany, Austria, Switzerland and Hungary were participating: 15 university hospitals, 20 state hospitals and 10 psychiatric departments of general hospitals. Some hospitals left the AMSP project during this time and therefore the total number of institutions taking part between 1994 and 2004 was somewhat higher (63 institutions). At some hospitals all patients are under AMSP surveillance whereas at other hospitals only selected wards take part.

Between 1990 and 1993 only few institutions participated. In order to obtain representative results and to prevent stochastic effects, we decided to begin our evaluation with the 1994 data.

From April 1994 to October 2004, a total number of 52,614 in-patients were filed.

Each year, data on the use of psychotropic and non-psychotropic drugs are gathered on two reference days in April and October. All drugs administered on these days are recorded along with age, sex and primary diagnosis of the patients. The daily dosage of all psychiatric and neurologic drugs is recorded as well.

Psychiatric diagnoses were recorded according to the WHO International Classification of Diseases (ICD-9 and ICD-10). In 1994, 3 hospitals still used ICD-9 and 6 hospitals ICD-10. By 2001, all participating institutions had changed to ICD-10. For the present study, all patients with the primary diagnosis of acute euphoric mania (ICD-9: 296.0, 296.2; ICD-10: F30.0-F30.9, F31.0-F31.2) and mixed-state/dysphoric mania (ICD-9: 296.4; ICD-10: F31.6) were identified and selected.

Psychopharmacological drugs were grouped into seven categories: lithium salts, anticonvulsants, antipsychotics,