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Use of concomitant medication with antipsychotic treatment in outpatients with schizophrenia: Results from the European Schizophrenia Outpatients Health Outcomes (SOHO) study

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Abstract

Use of concomitant medications with antipsychotic agents in the treatment of schizophrenia is common but lacks a clear scientific rationale. We evaluated concomitant medication usage during the first 6 months of the prospective, observational, European Schizophrenia Outpatient Health Outcomes (SOHO) study, examining its frequency, variation according to type of antipsychotic drug used, and impact on treatment tolerability. We also determined factors that were associated with concomitant medication use. The use of concomitant medications differed greatly among the countries participating in the SOHO study. The presence of depressive symptoms and being female were associated with the use of concomitant antidepressants. Certain antipsychotics were associated with less use of concomitant medications: significantly fewer olanzapine-, quetiapine- and clozapine-treated patients used concomitant anticholinergics or anxiolytics/hypnotics. Patients using concomitant medications had an increased incidence of sexually related side effects and extrapyramidal side effects (EPS) at 6 months follow-up compared with patients not using concomitant medications. The results should be interpreted conservatively due to the observational design of SOHO.
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1. Introduction

Antipsychotic medications are the principal pharmacological treatment for patients with schizophrenia, but other psychotropic drugs are also commonly used to treat this disorder. Despite the high frequency of concomitant medication use in daily psychiatric practice (Parepally et al., 2002; Sacristan et al., 2000), the rationale for this is unclear and based on few studies.

The most frequently prescribed concomitant medications in schizophrenia are anticholinergics, benzodiazepines,

Abbreviations: CGI, Clinical Global Impression; CGI-SCH, Clinical Global Impression-Schizophrenia; EPS, extrapyramidal side effects; GEE, generalised estimating equation; SOHO, Schizophrenia Health Outcomes Study.

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antidepressants, lithium and anticonvulsants. Anticholinergics are frequently prescribed for the treatment of extrapyramidal side effects (EPS). When used as concomitant medication, however, anticholinergics may worsen positive symptoms and decrease negative symptoms (Tandon and Dequardo, 1995), and are associated with impaired cognitive functioning of schizophrenic patients (Kasper and Resinger, 2003). Concomitant anticholinergic medication has also been assessed as a treatment for akathisia (Marsalek, 2000), and its effect on tardive dyskinesia is debatable (Soares and McGrath, 1997).

Investigations of benzodiazepines as adjunctive agents to conventional antipsychotic drugs have shown that they can reduce anxiety, insomnia, agitation, global impairment and psychotic symptoms (Stimmel, 1996; Wolkowitz and Pickar, 1991). Benzodiazepines are commonly used to treat neuroleptic-induced akathisia (Lima et al., 1999). The role of concomitant antidepressant treatment in schizophrenia is uncertain, but a recent Cochrane systematic review concluded that there was no convincing evidence to support or refute the use of antidepressants for the treatment of depression in people with schizophrenia (Whitehead et al., 2002).

Antiepileptic drugs are also used as concomitant medications in schizophrenia. Based on evidence from randomised clinical trials, the anticonvulsant carbamazepine cannot be recommended for routine use in the treatment or augmentation of antipsychotic therapy for schizophrenia (Leucht et al., 2002). A recent clinical trial showed faster clinical improvement in psychopathology when divalproex was added to risperidone or olanzapine than with either antipsychotic alone (Casey et al., 2003).

Not only is there a lack of evidence for the clinical effectiveness of concomitant psychiatric medications, but also clinicians must consider the safety and tolerability of concomitant medications when prescribing them. Polypharmacy is an important risk factor for clinically relevant adverse drug reactions (Fattinger et al., 2000; Beyth and Shorr, 1999).

The results presented in this paper are from the European Schizophrenia Outpatient Health Outcomes (SOHO) study, an ongoing 3-year prospective, observational study of the treatment of schizophrenia in the outpatient setting in Europe (Haro et al., 2003a, 2005; Lambert et al., 2005). The aims of the present analyses were to evaluate the frequency of concomitant medication use in schizophrenia, examine how it varies with the type of antipsychotic drug the patient is receiving, determine factors associated with concomitant medication use, and describe how the use of concomitant medication impacts on treatment tolerability.

2. Methods

The SOHO study is being conducted in 10 European countries (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) (Haro et al., 2003b). Local ethics committee approval was obtained in each country and all patients gave at least informed oral consent to participate in the study. Details of the study rationale, methods and recruitment have been published previously (Haro et al., 2003a).

2.1. Patient population

Participating psychiatrists were asked to include adult patients ($\geq$18 years) who had initiated or changed antipsychotic therapy for the treatment of schizophrenia in an outpatient, ambulatory or community setting, irrespective of the reason for the change. All patient care was at the discretion of the participating psychiatrist; no instructions or recommendations for the provision of care or pharmacotherapy (medication doses, medications changes, use of concomitant medication) were included in the study protocol.

The main objective of the SOHO study is to evaluate the cost effectiveness of treatment with olanzapine compared with other antipychotic medications in the treatment of patients with schizophrenia in the outpatient setting. The study includes patients taking any antipsychotic drug, but has a specific focus on the atypical antipsychotic olanzapine. In order to obtain more precise estimates of treatment outcomes with olanzapine, oversampling of this cohort was included in the study design. Therefore, the study was designed to provide two, approximately equal-sized, patient cohorts: (1) patients who initiated therapy with or changed to olanzapine; and (2) patients who initiated therapy with or changed to a non-olanzapine antipsychotic.

Participating psychiatrists were instructed to make treatment decisions before (and independently from) assessing each patient for enrolment. Different sample fractions entered each cohort to achieve approximately equal numbers in the two groups, leading to a stratified sample and oversampling of the olanzapine cohort.

2.2. Assessment of outcomes

Data were collected by psychiatrists during the normal course of treatment at the baseline assessment and at approximately 3- and 6-month follow-up. The following data were recorded: patient demographics, clinical course of schizophrenia, treatment, reason for treatment change, clinical severity, quality of life and social functioning. Clinical severity was assessed using a scale based on the Clinical Global Impression (CGI), which evaluated positive, negative, cognitive, depressive and overall symptoms on the day of assessment. This was subsequently expanded and validated as the Clinical Global Impression-Schizophrenia scale (CGI-SCH) (Haro et al., 2003c), which evaluates symptom severity during the week preceding the day of assessment. The CGI and CGI-SCH are physician-rated scales with values ranging from 1 (not ill) to 6 (among the

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