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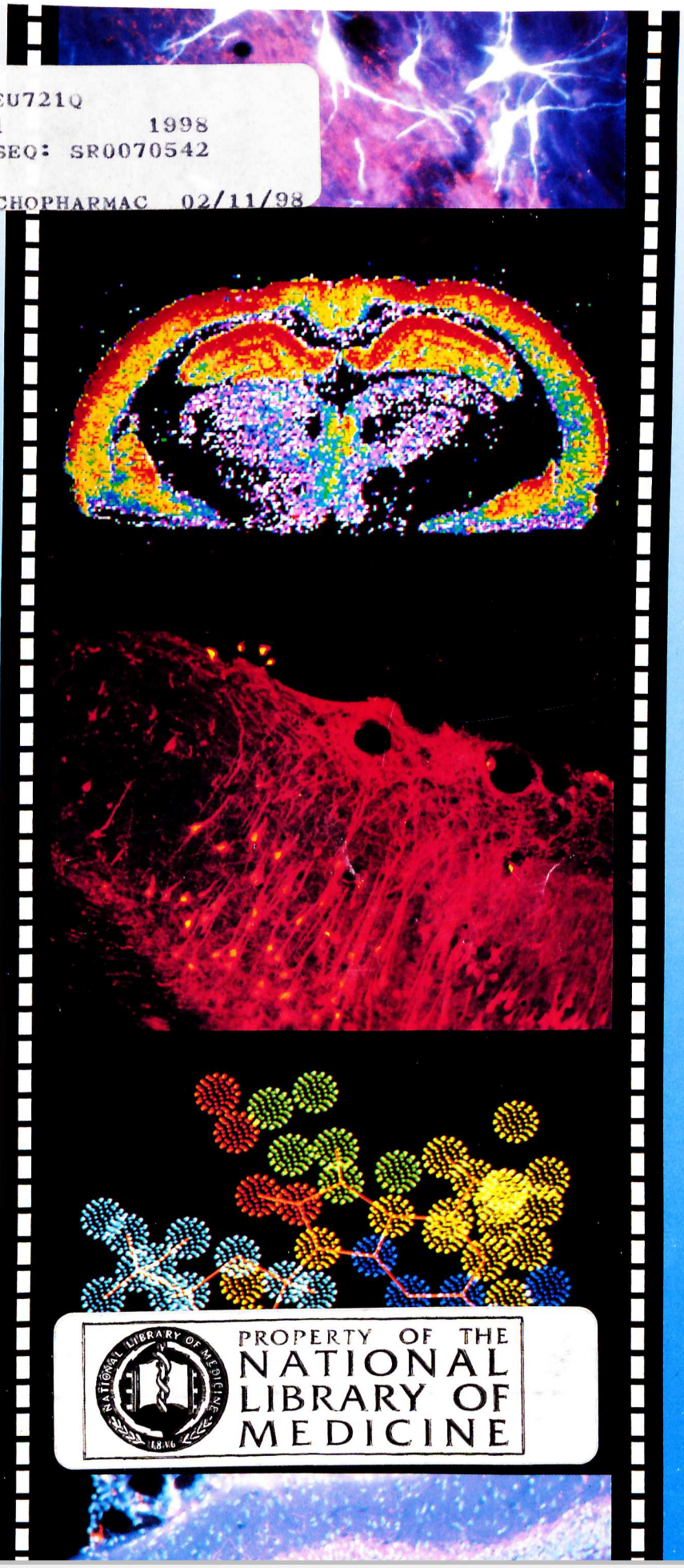

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EUROPEAN NEURO-PSYCHOPHARMACOLOGY

Guidelines for depot antipsychotic treatment in schizophrenia

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Abstract

These guidelines for depot antipsychotic treatment in schizophrenia were developed during a two-day consensus conference held on July 29 and 30, 1995 in Siena, Italy.

Depot antipsychotic medications were developed in the 1960s as an attempt to improve the long-term treatment of schizophrenia (and potentially other disorders benefiting from long-term antipsychotic medication). Depot drugs as distinguishable from shorter acting intramuscularly administered agents can provide a therapeutic concentration of at least a seven day duration in one parenteral dose.

The prevention of relapse in schizophrenia remains an enormous public health challenge worldwide and improvements in this area can have tremendous impact on morbidity, mortality and quality of life, as well as direct and indirect health care costs. Though there has been debate as to what extent depot (long-acting injectable) antipsychotics are associated with significantly fewer relapses and rehospitalizations, in our view when all of the data from individual trials and metaanalyses are taken together, the findings are extremely compelling in favor of depot drugs. However in many countries throughout the world fewer than 20% of individuals with schizophrenia receive these medications.

The major advantage of depot antipsychotics over oral medication is facilitation of compliance in medication taking. Non-compliance is very common among patients with schizophrenia and is a frequent cause of relapse. In terms of adverse effects, there are not convincing data that depot drugs are associated with a significantly higher incidence of adverse effects than oral drugs. Therefore in our opinion any patient for whom long-term antipsychotic treatment is indicated should be considered for depot drugs.

In choosing which drug the clinician should consider previous experience, personal patient preference, patients history of response (both therapeutic and adverse effects) and pharmacokinetic properties.

In conclusion the use of depot antipsychotics has important advantages in facilitating relapse prevention. Certainly pharmacotherapy

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must be combined with other treatment modalities as needed, but the consistent administration of the former is often what enables the latter. © 1998 Elsevier Science B.V./ECNP.

Keywords: Depot antipsychotics; Schizophrenia; Treatment; Relapse

1. Introduction

These guidelines were developed during a two-day consensus conference held on July 29 and 30, 1995 in Siena, Italy. The need for this effort was based on the recognition that the prevention of relapse in schizophrenia remains an enormous public health challenge world wide and that improvements in this area can have tremendous impact on morbidity, mortality and quality of life, as well as direct and indirect health care costs. Despite overwhelming evidence that non-compliance in medication-taking is a major contributing factor to unnecessarily high relapse rates, there is still inadequate attention being paid to strategies which can enhance medication acceptance and adherence, ranging from better psychoeducation directed at patients and families to the more extensive use of depot antipsychotic administration. Estimates suggest that in many countries throughout the world fewer than 20% of individuals with schizophrenia receive long-acting injectable medication. It is hoped that the promulgation of clear and concise guidelines for the use of depot drugs will help to remedy one important aspect of this problem.

1.1. Schizophrenia and the need for long-term treatment

Schizophrenia is a chronic illness usually beginning in late adolescence or early adulthood. The condition is characterized by remissions and exacerbations, though a proportion of patients remain persistently ill. There is evidence that after 10 to 20 years some patients may improve in terms of their overall level of psychopathology and community adjustment. The disease affects 1% of most populations of the Western World, but consumes a disproportionate share of health care costs. A large number of persons with schizophrenia are permanently disabled, and in many countries, homeless.

The risk of suicide may be as high as 1 in 10, particularly in the early years after illness onset and among males (Miles, 1977; Drake et al., 1984). Mortality is also higher due to accidental deaths and other causes (Bland et al., 1976). Patients suffering from this illness often receive sub-optimal general medical care and frequently have undiagnosed comorbid medical conditions.

The treatment of schizophrenia requires an integration of biologic, psychologic and psychosocial perspectives. There is increasing evidence that early diagnosis and appropriate treatment can improve long-term outcome (May et al., 1981). Antipsychotic drugs are a critical modality in

and relapse prevention. These drugs cannot only alleviate or improve psychopathology, but may also enhance psychosocial and vocational adjustment and improve subjective well being. Although medications can be highly effective, response varies and some patients derive considerably less benefit than others. Despite heterogeneity in drug responsiveness, antipsychotic drugs are indicated for all patients with schizophrenia.

Long-term treatment with medication is critical in optimizing outcome and is the focus of these guidelines.

1.2. Definition and measurement of relapse

The participants defined relapse as "the appearance, reappearance or exacerbation of symptoms (typically psychotic) of schizophrenia which may require a change in clinical care."

When a relapse is observed, clinicians should make a differential diagnosis and assess possible contributing factors, e.g. natural course of the illness, non-compliance, underdosage (or drug discontinuation), stress, comorbid conditions, drug abuse, medical illness, adverse effects, etc.

Alternative clinical interventions should be considered such as increased surveillance or intervention of a psychotherapeutic/psychosocial or pharmacotherapeutic nature (e.g. reinstitute drug treatment, increase dosage, prescribe adjunctive pharmacotherapy, change antipsychotic).

Given the fluctuating course of this illness, an important aspect of treatment focuses on the maintenance of therapeutic gains and the prevention of clinical exacerbation, relapse and rehospitalizations. This is a concern not only because of the immediate personal and psychosocial disruption, but also because frequent relapses can increase the likelihood of poorer long-term outcome.

The definition of relapse has been an important variable in studies of long-term treatment in schizophrenia. The basis on which we strongly recommend continued antipsychotic drugs is the significant reduction in relapse rate (despite variability in definition) across numerous studies with treatment as compared to untreated cases or placebo-treated controls. The manner in which relapse is defined, however, takes on critical importance in understanding the clinical implications of those findings as well as making comparisons across studies. The efficacy of specific treatment strategies may vary depending upon what definitions of relapse are applied.

Gilbert et al. (1995) recently reviewed 66 studies

studies did not provide any definition of relapse. In 11 studies relapse was defined as "a return to active medication". The remaining 33 studies defined relapse as either the emergence of "behavioral worsening" (with agitation, aggression, insomnia, anxiety, hallucinations, delusions, or assaultive or suicidal behavior). Some of these investigations utilized a specified change seen on particular items on a clinical rating scale such as the Brief Psychiatric Rating Scale (BPRS). In one large scale study (Schooler et al., 1995), psychotic relapse was defined by a rating of "moderate" or greater representing an increase of at least two scale points on any of five psychotic items of the BPRS (conceptual disorganization, grandiosity, suspiciousness, hallucinatory behavior and unusual thought content). This increase in psychotic symptoms had to persist for two successive scheduled ratings separated by four weeks or a scheduled rating and an unscheduled rating associated with the initiation of open (non-blind) active medication.

Similar criteria were employed by Kane et al. (1983) in a previous study. Marder et al. (Marder et al., 1984, 1987) defined three levels of unfavorable outcome that would lead to an antipsychotic dosage increase. When patients had an increase of 3 or more points on the BPRS cluster scores for thought disturbance or paranoia they were considered to have had a "psychotic exacerbation". These exacerbations were relatively mild and seldom led to rehospitalization. Clinicians were allowed to essentially increase the dosage by up to 100%. If symptoms could not be adequately controlled within this range, they were considered to have had a "relapse". The third level of outcome was rehospitalization. Those criteria for relapse, therefore, not only involved an objective measure of worsening psychopathology, but also failure to respond to a specified clinical intervention.

As can be seen from these examples in defining relapse, a number of key factors need to be considered:

1. Absolute degree of increase in psychopathology
2. Nature of psychopathology increasing (i.e. psychotic or non-psychotic)
3. Degree of increase in psychopathology relative to the "baseline" state of the patient
4. Duration of the exacerbation
5. Response of the exacerbation to treatment intervention (which may be pharmacologic and/or non pharmacologic)

The critical question in attempting to define relapse is the desired balance between specificity and sensitivity. This judgment will in turn be influenced by the relative risk associated with acting on the basis of a false positive and not acting on the basis of a false negative. The potential consequences of a relapse for that given individual based the ultimate clinical judgment. Though at present we are not aware of significant risks associated with treatment of a false positive "relapse", there is some reason to be concerned about unnecessary increases in antipsychotic drug dosage in relation to the development of tardive dyskinesia (Kane, 1995).

Definitions of relapse which can be used by clinicians in routine practice will never be a substitute for experienced clinical judgment, but can provide a useful frame of reference for organizing and systematizing the decision making process.

1.3. Benefits and risks of neuroleptic maintenance treatment

Several extensive reviews have appeared in recent years summarizing the data on the impact of continued antipsychotic medication on rates of relapse in schizophrenia (Davis et al., 1989; Gilbert et al., 1995). There is overwhelming evidence that the use of medication can have a significant (clinical and statistical) benefit in improving outcome. The consequences of relapse are diverse and often unpredictable ranging from loss of confidence and self-esteem, disruption in psychosocial and vocational adjustment and family burden to risk of suicide or aggressive behavior. There is no question that relapse is associated with substantial increase in the costs associated with the illness (both direct and indirect). In addition, there is some suggestion that with each subsequent episode time to recovery and degree of recovery are not as good previously. It is possible that this reflects the natural course of the disease as well, but prevention of relapse is a goal which may have long-term impact on the ultimate course of the disease.

The risks associated with long-term neuroleptic treatment are largely those related to a variety of adverse reactions, particularly neurologic effects such as tardive dyskinesia or tardive dystonia. Other side effects such as drug-induced parkinsonism, akathisia, weight gain and sedation can also pose problems to some patients.

Those adverse reactions which are of most concern in terms of potential-seriousness and persistence are the abnormal involuntary movement disorders associated with long-term neuroleptic treatment. Although prevalence estimates vary widely, on average 15–20% of patients chronically-treated with neuroleptic medication manifest some degree of tardive dyskinesia (Kane et al., 1992). Incidence studies (Kane, 1995; Glazer and Kane, 1992) suggest that approximately 5% of young to middle-aged adult patients develop some evidence of abnormal involuntary movements with each year of neuroleptic treatment. The majority of these cases are mild and nonprogressive and a substantial proportion can in fact improve or remit entirely if neuroleptic dosage is reduced (Kane et al., 1992) or they are switched to a drug such as clozapine

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