FC58-4

RECOVERY IN AFFECTIVE DISORDER — A CASE REGISTER STUDY

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Background: It is unclear how the duration of episodes changes during the course of unipolar and bipolar affective disorder.

Method: The rate of recovery was estimated with survival analyses at successive episodes in a case register study including all hospital admissions with primary affective disorder in Denmark during 1971–1993.

Results: A total of 9,174 patients with recurrent episodes were followed from their first admission. The rate of recovery did not change with the number of episodes in unipolar or in bipolar disorder. This result is in accordance with findings from recent decades whereas the majority of studies from the era before the introduction of effective treatment have found an increasing duration of episodes during the course of illness.

Conclusion: The duration of episodes in untreated unipolar and bipolar affective disorder seems to increase as the illnesses progress whereas in modern treatment settings it is possible to stop this deteriorating course.

FC58-5

MORTALITY IN ADOLESCENTS ADMITTED WITH A DIAGNOSIS OF AFFECTIVE DISORDER (DEPRESSION AND BIPOLAR DISORDER)

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Objective: To study the mortality in a large, nation-wide cohort of adolescents admitted with depression.

Methods: Using the Nation-wide Danish Psychiatic Case- Register, the study analyzes all adolescents, aged 13–19 years, who had been admitted to a psychiatic department during the years 1970–93. Combining with information from the nation-wide Death register, the prognosis, as regards mortality, was described.

Results: Compared to an age- and sex-standardized group form the normal population, the cohort had a considerable increased mortality. The SMR (standardized mortality ratio) was 5.54 for males (CI 3.71–7.96), and 8.76 for females (CI 5.76–12.93). The SMR for suicide was 19.85 for males (CI 12.44–30.05) and 37.77 for females (CI 23.07–58.33). The distribution of death causes and the time from admissions to death will be presented.

Conclusions: Adolescents diagnosed with affective disorders are at great risk for premature death. The treatment implications will be discussed.

FC58-6

TREATMENT OF ACUTE MANIC EPISODES WITH VALPROATE AS AN ADJUNCT TO NEUROLEPTIC MEDICATION

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In a multicentre randomised double-blind trial 136 patients hospitalised for acute manic episodes (ICD 10) received either 20 mg/kg sodium valproate (Orfiril®) or placebo in addition to basic treatment with neuroleptics for 21 days. Investigators were required to reduce the dosage of the individual neuroleptic on day 5, 10 and 15 by one third of the last dose administered or according to the clinical condition. Psychopathological ratings by means of the Young Mania Rating Scale, Global Assessment Scale (GAS) and Clinical Global Impression (CGI) were performed at various time points. The safety was evaluated on the basis of the occurrence of adverse events. The total dosage of neuroleptics expressed as haloperidol-equivalents was the primary target parameter.

The neuroleptic dose (haloperidol-equivalents) declined continuously in the valproate group from 14.3 ± 9.4 mg on the first study day to 8.2 ± 6.9 mg on the last day, while values varied in the placebo group between 12.0 ± 6.6 mg and 10.4 ± 9.6 mg. A statistically significant difference in the daily neuroleptic dose was found for the second and third study weeks ($p = 0.0007$, two-tailed). The severity of manic symptoms decreased in the course of the study from 30.9 ± 8.1 to 11.6 ± 9.3 and from 30.9 ± 8.4 to 17.9 ± 10.9 in the valproate and placebo group, respectively ($p = 0.0042$). Mean GAS scores increased from 40.4 ± 10.3 to 63.8 ± 16.3 in the valproate group and from 41.0 ± 10.8 to 56.7 ± 18.7 in the placebo group ($p = 0.0108$).

18 patients dropped out prematurely, 7 of the valproate group and 11 of the placebo group. No serious adverse events occurred. The combination of valproate and neuroleptics was well tolerated and did not lead to increased occurrence of adverse events. In conclusion, the study clearly demonstrates the clinical effectiveness and safety of valproate as an adjunct to neuroleptic medication in patients with acute manic episodes.

FC58-7

A COMPARISON OF SYMPTOMS FOLLOWING TREATMENT INTERRUPTION: EVIDENCE FROM A RANDOMIZED, DOUBLE-BLIND TRIAL WITH FLUOXETINE, SERTRALINE, AND PAROXETINE

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Introduction: Evidence suggests that shorter acting SSRIs compared with fluoxetine are often associated with increased adverse events and dysphoria during brief treatment interruptions. Previous studies are limited by lack of prospective patient randomization; only one was conducted under controlled conditions. We report a prospective, randomized, double-blind study assessing effects of SSRI interruption following successful initial treatment of depression.

Methods: Drug-free outpatients (N = 284) with major depression were randomized under double-blind conditions to fluoxetine, sertraline, or paroxetine treatment. Responders following 4–10 weeks of acute treatment (N = 213; fluoxetine = 67, sertraline = 75, paroxetine = 71) went into a 5-month continuation phase. Treatment was then interrupted for 4–6 day periods under double-blind conditions. Adverse event (AEs) were solicited by systematic inquiry.

Results: Before treatment interruption, all groups had similar AEs and HAMD scores. Following interruption, new or worsened AEs were more frequent among paroxetine-treated than fluoxetine-treated or sertraline-treated patients ($p < .001$, $p = .006$; respectively) and showed a trend for greater frequency among sertraline-treated patients compared with fluoxetine-treated patients ($p = .086$). Paroxetine-treated patients showed a trend for return of depressive symptoms compared with fluoxetine-treated patients ($p = .074$).

Conclusion: These results provide evidence from a prospective, randomized, double-blind study that brief interruption of SSRI

treatment may be associated with new or worsened AEs (frequency of AE reports: paroxetine > sertraline > fluoxetine).

S59. Optimising drug therapy in various psychiatric conditions

Chairs: DM Taylor (UK), J Donoghue (UK)

S59-1
OPTIMAL USE OF CLASSICAL (TYPICAL) ANTIPSYCHOTIC DRUGS

D. Branford. *Leicester Frith Hospital, Glenfrith Division of Fosse Health NHS Trust, Leicester, UK*

For nearly 50 years the typical antipsychotic drugs have remained the drugs of choice for treatment of schizophrenia. During that 50 year period different concerns have dominated opinions about their optimal use. These include extrapyramidal side effects, tardive dyskinesia, sudden death, neuroleptic malignant syndrome, non-compliance, hormonal disturbance and excessive doses, just to mention a few. In addition there have been controversies about the need for the coprescribing of anticholinergic drugs, the efficacy of polypharmacy, the safety of chlorpromazine and the prescribing of antipsychotic drugs both for the elderly and in mental retardation to control challenging behaviours. This presentation will provide a historical overview of these controversies and issues, in order to propose guidelines for the optimal use of antipsychotic drugs.

S59-2
OPTIMAL USE OF ATYPICAL ANTIPSYCHOTICS

C. Paton. *Bexley Hospital, Oxleas NHS Trust, Bexley, Kent DA5 2BW, UK*

Atypical antipsychotics have an improved side-effect profile over the older traditional drugs, while demonstrating at least equal efficacy against positive, negative and co-morbid mood symptoms. Clinical trials demonstrating these effects have employed atypical drugs as monotherapy, with optimal anticholinergic use, in a cohort of patients not selected for treatment refractory illness.

Because of the relatively high cost of atypicals, they are frequently reserved in clinical practice for patients who fail to respond to the older drugs. The result is maximum licensed doses being used routinely, along with concurrent antipsychotics and anticholinergics. The use of atypicals in this way leads to high prescribing costs with low clinical returns. Audit is a useful tool which can be used to improve understanding and practice in this area of prescribing, and maximise the tangible benefits to patients that the new atypical antipsychotic drugs offer.

S59-3
OPTIMAL USE OF CLOZAPINE

D. Taylor. *The Maudsley Hospital, Denmark Hill, London SE5 8AZ, UK*

This session will examine methods of optimising efficacy and tolerability when using clozapine. Dosing and plasma-level issues will be covered and supporting data presented. The management of adverse effects will also be examined and the benefits of remedial treatments discussed. Pharmacokinetic aspects will also be outlined and their relation to adverse interactions examined in depth.

S59-4
OPTIMAL USE OF MOOD STABILISING AGENTS

L. Haygarth. *High Royd's Hospital, Leeds Community & Mental Health Trust, Menston, Ilkley, West Yorks LS29 6AQ, UK*

The optimal use of mood stabilising agents represents a considerable challenge to the clinician. The majority of pharmacological therapies, now used as mood stabilisers, were first developed for other indications. Current mood stabilisers include lithium, antipsychotics, carbamazepine, sodium valproate, other anticonvulsants, thyroid hormones and calcium channel blockers. Lithium is the most widely recommended for the treatment of bipolar affective disorder. Unfortunately, its effectiveness in clinical practice, is less than that predicted from controlled trials. A major cause of treatment failure is attributed to patient non-compliance. Patient education, combined with due attention to side effects and monitoring criteria may well produce an increase in response.

Definitive data on the primary mode of action of mood stabilisers is not readily available with those compounds used showing no single pharmacological property. However, the pharmacokinetics and pharmacodynamics of all the compounds used, are well studied. For optimal therapy it is important to consider these parameters of the individual drugs. As mood disorders can be resistant to treatment with a single agent, polypharmacy is common. Particular reference must be paid to potential drug interactions and increased side effects, which may result in treatment failure.

S59-5
OPTIMAL USE OF ANTIDEPRESSANTS

J. Donoghue. *Clatterbridge Hospital, Bebington, Wirral, L63 4JY, UK*

Guidance on the effective treatment of depression has been issued at both national and international level. To achieve optimal outcomes, treatment should be initiated at an early stage, be vigorous, and continue for 4–6 months after a response has been obtained.

There is considerable evidence that too often, none of these objectives are achieved in practice, with consequent poor outcomes for patients.

Pharmacoepidemiological research findings consistently suggest that patients treated with older tricyclic antidepressants rarely complete an effective course of treatment - either in terms of obtaining an adequate dose of antidepressant, or completing a minimum period of treatment if an adequate dose is achieved.

Initial choice of antidepressant appears to be an important factor in determining subsequent treatment patterns: patients who initiate treatment with a selective serotonin reuptake inhibitor (SSRI) are considerably more likely to complete an effective course of treatment - which should be reflected in better outcomes. Concerns have been raised about the added costs that this approach to treatment would entail, however, research to date has failed to show that tricyclic antidepressants are more cost-effective than SSRIs, despite the difference in costs of these medicines.

It is likely that a shift to the use of SSRI antidepressants as first choice drug therapy for depression would have a significant impact on improving outcomes, without increasing total costs.

https://doi.org/10.1016/S0924-9338(99)80260-0 Published online by Cambridge University Press