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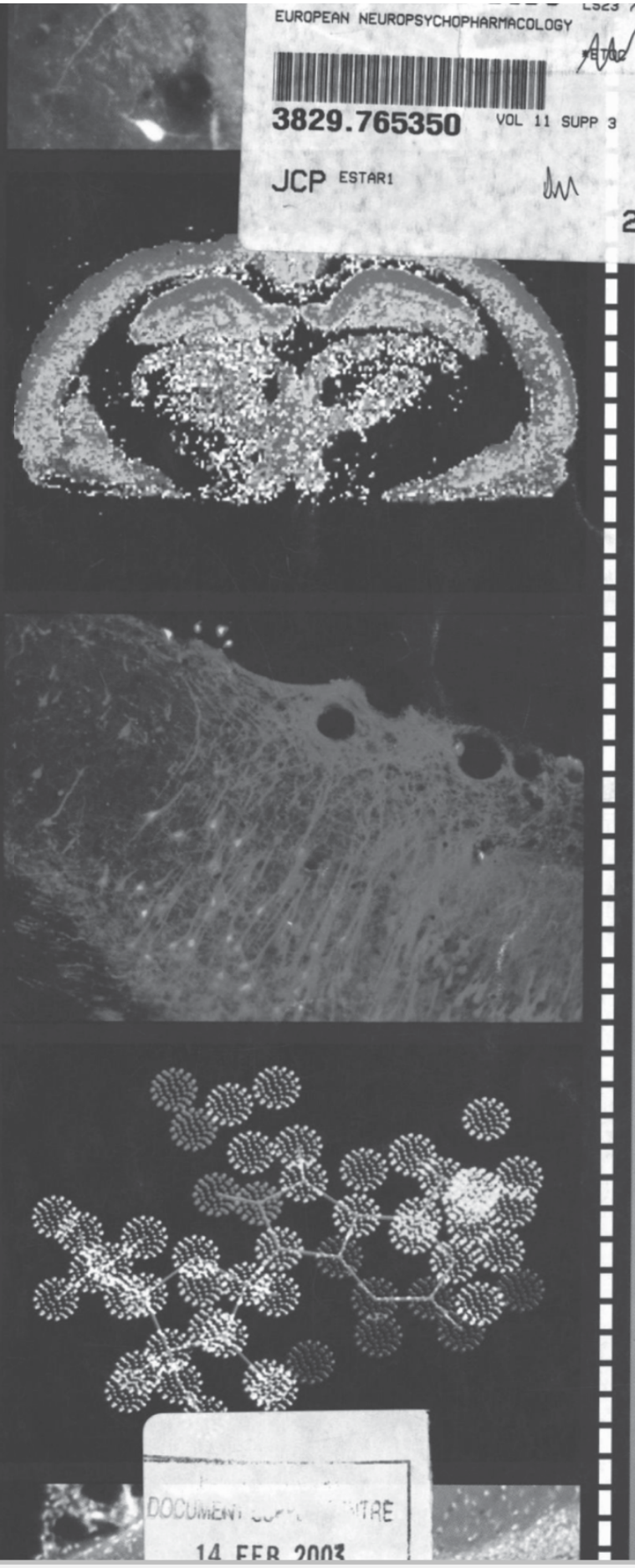

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supersensitivity mania, rendering Lithium treatment more and more ineffective (H. Himmelhorth, in J.C. Soares & S. Gershon, 2000). Furthermore, prior polypharmaceutical course of treatment, especially antidepressants, contributes to Lithium resistance. Withdrawal rebound can make Lithium ineffective or counterproductive. Finally: "treatment with Lithium for less than two years is either of negligible benefit or of actual harm to bipolar patients. A too short term treatment may be worse than useless. Three years is probably the minimum length" (G.M. Goodwin, 1994). Therefore, the prescription of Lithium in acute mood episodes is warranted. This decision must nonetheless be well thought over, taking into account a long-term strategy with the perspective of prolonged Lithium treatment, principally to stabilize mood oscillations, prevent or counteract ongoing cerebral damage, and prevent suicide.

Indeed, on the long term, Lithium has many beneficial effects: against suicidal behaviour, viral infection, and more interestingly, against neurodegeneration (H.K. Manji *et al.*, 2000). The treatment's perspective is thereby broadened to neuroprotection, neurogenesis, and management of pathological brain aging.

There are several other drugs used to treat mania, with a more rapid efficacy. These can represent an alternative choice. Again, the decision to use Lithium, alone or combined with other drugs in acute mood episodes, must take into account a long-term strategy and the long-term beneficial effects.

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S.13.03 Typical and atypical antipsychotics in the treatment of mania

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For many years, antipsychotics have been the cornerstone of treatment for acute mania in Europe. It provoked surprise, and not a little consternation, therefore, that in influential US guidelines, antipsychotics were defined to be *adjunctive*, not first line, in the management of mania. The first line drugs were declared to be mood stabilisers (1). The term mood stabilizer is imprecisely defined but carries a reassuring ring. It is bestowed on lithium for the good reason that there exists clear evidence that it prevents recurrence and relapse in the long term. The term is conferred upon the anticonvulsants on the basis of much less convincing evidence. Although divalproex certainly has equal efficacy to lithium in the treatment of acute mania (2), in long term maintenance the results were inconclusive (3).

The basis for the distinction between mood stabilisers and adjunctive treatments was always opinion, rather than evidence. There is an excellent controlled comparison of the gold standard mood stabiliser, lithium with the original antipsychotic, chlorpromazine, which showed an advantage to chlorpromazine in highly active manic patients (4). This data accords with clinical experience and indeed with audits of clinical practice internationally, which all illustrate the widespread, perhaps universal use of antipsychotic drugs, often at quite high doses. Severe mania may demand the actions that only antipsychotics can produce.

A greater challenge comes from the development of the atypical antipsychotics and the realisation that lower doses of the classical drugs are preferable in the treatment of schizophrenia because of the severity of adverse effects. We remain a little uncertain whether the central action that is sought in acute treatment of mania is primarily the chemical straightjacket of antipsychotic overdose. The classical antipsychotics certainly reduce demands on staff (4) by controlling behaviour. The atypical antipsychotics will not have the same side effect burden. Will they prove to be as useful as the older drugs? How we balance the interests of staff and patients, suggests the need for new approaches to assessing outcome in treatment trials, and more emphasis on the patient experience.

The new trials we already have are interesting because they suggest that atypicals can produce antimanic effects that are certainly superior to placebo and probably additive to the action of so-called mood stabilisers like divalproex and lithium. This is already suggested by studies of risperidone and olanzapine. Indeed combination treatments are extremely common in practice and may allow the balance between efficacy and side effects to be optimised in acute and long term treatment.

There is the further issue of whether atypical antipsychotics are themselves 'mood stabilising', and whether the meaning of that term is in need of re-statement. Certainly clozapine has a reputation and some evidence to support a potent action in the rapid cycling states where mood instability is a defining feature.

We are at a stage of rapid and incremental growth in available information because of the efforts of companies to identify the actions of their still new compounds. The greater challenge is to integrate the increasingly wide range of choices into coherent clinical planning and humane treatment of a difficult condition. These are challenges primarily for clinicians, not for industry, and can only be addressed by the growth of the trial culture within everyday practice.

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S.13.05 Treatment of mixed episodes

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Mixed episodes challenge clinicians and researchers to assess and treat a condition defined by frequent fluctuation of signs and symptoms. Terms such as Bipolar Disorder and Manic-Depressive