regime. In the absence of such evidence, Dr. Haider can firmly claim that a single evening dosage of sustained release amitriptyline is an advantage over the thrice daily dosage of ordinary amitriptyline, used in current therapy.

2. A very important point has been ignored, or perhaps has been unappreciated by Dr. Rifkin and his colleagues, that equal therapeutic effect is obtained in the case of the sustained release form at two-thirds of the dosage of ordinary amitriptyline. Clinical trials have demonstrated this. Sims (1972), Gomez (1972), Wheatley (1972), Sedman (1972). This represents a definite advance, especially with regard to psychotropic drugs.

3. Reference to the effectiveness of imipramine given in single dosage is based on a retrospective and somewhat impressionistic study covering 43 patients by one of the co-authors (Dr. D. F. Klein) at their own hospital. This study, and your correspondents' interpretation thereof, are open to criticism on the following points:

(a) Findings with imipramine cannot be taken to imply that amitriptyline given in single daily doses would necessarily produce similar results. This is especially true in regard to side effects.

(b) Data are retrospective in both groups studied. In the first group 12 or 22 subjects received concomitant drugs, several of which would inevitably influence the outcome of the patient's depression. All patients in this first group had psychotherapy.

(c) We are not told how the patient's progress was assessed.

(d) The authors' claim that a single daily dosage of imipramine 'can give fewer side effects' is based on data (unstated) from *three* patients.

4. Dr. Rifkin *et al.* ignore the important point that even if one were to give ordinary amitriptyline as a single dose and attempt to compare it with the same or two-thirds of the dose of the sustained release form, there could be no true comparison, as the two formulations are quite different. One is a normal film-coated compressed tablet of amitriptyline hydrochloride, the other is a gelatine capsule containing the active principle in small coated pellets each of which is a microdialysis unit diffusing out a fixed amount of drug over a specified period. A much more sophisticated process than ordinary tablet disintegration is surely an advance by any standards.

My Company is, of course, aware that both forms of amitriptyline should be compared in a once daily dosage, and are at present conducting such clinical studies.

Lastly, I would remind Dr. Rifkin and his colleagues that the object of Dr. Haider's study was not to demonstrate an advantage over ordinary amitriptyline given in an empirical and as yet unproved dosage, but to show that sustained release amitriptyline given once a day and producing equal therapeutic effect at two-thirds of the dosage of ordinary amitriptyline on a thrice daily dosage basis is an advance in the treatment of depressive illness.

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FLUPENTHIXOL IN THE TREATMENT OF DEPRESSIVE STATES

DEAR SIR,

In a recent report on the treatment of chronic schizophrenia with flupenthixol decanoate (1), 11 of the 13 schizophrenic patients whom we treated reported a significant elevation of mood. We suggested that flupenthixol might therefore prove useful not only as an antipsychotic drug but also as an antidepressant, and similar suggestions had been made previously in the columns of your *Journal* (2, 3).

We subsequently treated 25 patients suffering from sustained depression of mood, average duration of depression being 7·5 years. Twenty patients showed diurnal variation of mood, 21 depressive hypochondriasis, 15 depressive sleep disorder and 14 psychomotor retardation. Twelve had made suicidal attempts and most of them were regarded as suffering from long-standing 'mixed' depressive illnesses (i.e. showing both 'endogenous', 'reactive' and neurotic features). Twenty were female, 5 male, and mean age was 47 years (range 18·78 years). All but one had previously been treated with various tricyclic antidepressants and 14 with monoamine oxidase inhibitors, whilst 14 had been treated with electroplexy.

Sixteen patients were treated with oral flupenthixol at a dose of 0·5–2 mg. per day, and 9 with flupenthixol decanoate 20–40 mg. intramuscularly every 2–3 weeks. Of the latter, 5 developed parkinsonism

(which in all cases responded uneventfully to orphenadrine citrate). Patients treated with oral flupenthixol reported no side effects except for a tendency to early insomnia. Medication was therefore given in two divided doses in the morning and lunch-time, each combined with Valium 2 mg., and sleep returned to normal.

Twenty patients reported a good or excellent improvement in their symptoms—particularly in inertia, retardation and anorexia—within a fortnight of starting medication. We consider that our patients were chronically and unequivocally depressed, and as they had had a variety of previous unsuccessful treatments could hardly be regarded as 'placebo reactors'.

Our results, although uncontrolled, seem to support our previous suggestion that flupenthixol may prove an effective antidepressant; and its marked lack of side effects when given orally and the possibility of depot treatment in patients otherwise liable to take overdoses of drugs with suicidal intent would present considerable practical advantages. Other advantages would be the absence of dietary restrictions, the possibility of combining flupenthixol with tricyclic or MAOI antidepressants, and its use in depressive conditions in the elderly where the autonomic side effects of conventional tricyclic antidepressants are often tiresome and occasionally dangerous. No evidence of addiction or dependence was seen, although this is a theoretical possibility which would have to be borne in mind in any drug with such a clear mood-elevating effect. Caution would also be required in very severely depressed patients where the possibility of decreased sleep and increased drive would have obvious dangers. We feel that further controlled and comparative trials are indicated, and these are being planned.

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FLUPENTHIXOL AND THE OUT-PATIENT MAINTENANCE TREATMENT OF SCHIZOPHRENIA

DEAR SIR,

I am sure that my friend Dr. Carney will forgive me when I suggest that his letter on long-acting neuroleptics over-simplifies the situation (*Journal*, October 1972, **121**, 458). The reasons why patients discontinue these regimes or become lost from them are extremely complex. Dr. D. A. W. Johnson and myself have analysed a series of such defaulters, and the results are to be published shortly in *Psychological Medicine*. One thing which emerges clearly is that the presence of extrapyramidal or other side effects is only one of the factors concerned, and by no means the most important.

In our own experience with long-acting fluphenazine, which now extends over more than six years, we have experienced nothing like the degree of difficulty with side effects which Dr. Carney reports. Following his letter, I have looked at the last 300 patients who have come into the maintenance programme with fluphenazine decanoate. Of these, not more than six could have been regarded as having to discontinue the regime primarily because of extrapyramidal side effects. Even for some of these cases the situation was complicated by personality or social factors, without which treatment might have continued satisfactorily.

With further experience, we have found in our service that a much greater degree of flexibility is required in maintaining a regime of long-acting injections than had been thought necessary earlier on. If the dose of injections, the timing of injections and the prescription of anti-parkinsonian tablets are suitably adjusted, there are very few patients indeed who cannot be satisfactorily maintained on this regime. As far as the results are concerned, the preliminary figures from our sample already show a dramatic fall in the necessity for re-admission to hospital (1).

Like other colleagues, I find it difficult to understand Dr. Carney's strength of emphasis on depression as a complication in this form of treatment; I don't think there has been lack of clinical sensitivity on our part. In the whole of our experience with this programme, only three suicides have occurred, none of which could have been regarded as wholly due to a depressive reaction. Suicide in schizophrenia is a very much more complicated question than this, and one is more likely to reduce the rate by effectively treating schizophrenia than by withholding essential forms of medication. In fact, the MRC double-blind trial reported by Gaind at Montreal last May showed that only 10 per cent of the patients on fluphenazine decanoate injections required antidepressants compared with 14 per cent of those on placebo.

From the figures given by Dr. Carney, I cannot accept that he is reporting a lower rate of significant side effects than would be found with a well-supervised programme of fluphenazine depot injections. Although my own experience with flupenthixol is limited, I