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Monoamine Oxidase Inhibitors

DEAR SIR,

Dr Pare's article on 'The Present Status of Monoamine Oxidase Inhibitors' is one of a genre that marks the renaissance of these drugs (Murphy *et al*, 1984; White & Simpson, 1985).

This is understandable given that the 'second generation' compounds are less exciting than hoped, that early use of phenelzine was often with inadequate dosage and that improved diagnostic criteria give some (still scanty) hope that the elusive 'MAO' responder might be found.

There appears also to be a naive and wishful assumption that because their therapeutic potential may have been underestimated the side effects of MAOI were exaggerated. It would be more logical to conclude that adequate dosage and effective treatment might also increase the incidence of side effects above placebo level.

This point may be illustrated by referring back to the original work that Professor Marley and I conducted during a three year period, more than 20 years ago (Blackwell *et al*, 1967). A careful epidemiologic assessment of the risk for hypertensive crises in the contained population of a single hospital revealed that 8% of patients on tranylcypromine experienced the problem compared to 1·5% of those on phenelzine. Analysis of prescribing data showed that episodes on phenelzine occurred at higher dosage after longer duration of treatment, suggesting what has now been confirmed about the significance of adequate treatment. This observation was used as the basis for a carefully conducted clinical pharmacology experiment in which the hypertensive effects were shown to be related to the duration of treatment, proximity and dosage of phenelzine antecedent to a food challenge.

A recent prospective controlled comparison (Rabkin *et al*, 1984) was made of the incidence of serious side effects in patients taking phenelzine, imipramine or placebo. Like the earlier study (Blackwell *et al*, 1967) it was conducted in a university research clinic by experts in psychopharmacology.

The incidence of hypertensive crisis on phenelzine was exactly the same (8%) as previously reported with tranylcypromine. Eleven patients suffered a hypertensive crisis of whom six ate tyramine containing foods 'despite meticulous dietary review and cautioning' and three took ephedrine-containing medication. Four of the eleven patients obtained emergency medical treatment and a fifth was hospitalised in coma with intracranial bleeding due to an unsuspected aneurysm.

What may happen in less carefully supervised environments is suggested by a report from a British counseling service (Wright, 1978). Despite warnings about foodstuffs and cold remedies thirty-five out of one hundred and nineteen patients suffered hypertensive crises of which four were fatal.

Wide discrepancies in the reported incidence of side effects are contributed to by pendulum swings from early over-reporting to later under-reporting. The way to truth is not to average good and bad data (gleaned from meaningless prescribing statistics and manufacturers myopic files) but to sift the wheat from the chaff. Based on the (to my knowledge) only 2 carefully conducted studies my own conclusions differ markedly from Dr Pare's view that the risk of hypertensive crisis has been exaggerated. These conclusions are:

1. In carefully observed university settings patients treated with adequate therapeutic dosages of an MAOI and warned to avoid foodstuffs and ephedrine medications the risk of hypertensive crisis is 1 in 12 (8%).
2. It is impossible to predict which individual patients will be compliant (Blackwell, 1976) but about half will have unavoidable memory lapses. Fear-provoking messages are not likely to reduce the problem since they often facilitate forgetting.
3. Any patient with adequate MAO inhibition will experience hypertension if he ingests enough tyramine or any of the indirectly acting amines. A majority of these will remain unaware of raised blood pressure but a small minority will suffer serious consequences.

The risks of MAO inhibitors are not confined to this one side-effect. In the study cited above (Rabkin *et al*, 1984) the incidence of severe side effects was 14% on placebo, 27% on imipramine and 64% on phenelzine. With phenelzine these were hypomania (10%), hypertensive crisis (8%), weight gain over fifteen lbs. (8%) and anorgasmia or impotence (22%). Treatment over time revealed that by thirty-three weeks less than half the imipramine patients

suffered a serious side effect compared to over 90% of phenelzine treated patients. Thirty eight per cent of patients had two or more serious side effects and all except one were taking phenelzine. Altogether 132 major side effects were recorded for 141 patients treated with phenelzine.

The risks of MAO inhibitors will be further increased in an era of 'prophylaxis' and long-term treatment. Recent studies have shown that withdrawal effects are more serious than with tricyclics (Tyrer, 1984) and overdose is extremely difficult to manage (Linden *et al*, 1984).

The most remarkable feature of the above study was that in a second article (Rabkin *et al*, 1984) the authors were able to conclude that 'MAO inhibitors when properly prescribed are safer than is often believed'. This chemophilic conclusion seems to be supported by Dr. Pare's treatment of the risk to benefit ratio for these drugs. For the sake of the patients to whom we prescribe I hope that a more careful view will prevail so that we learn from the lessons of history without repeating them. This is the second time around for the MAO inhibitors but the millenium has not arrived.

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Cyproheptadine and Antidepressant-induced Anorgasmia

SIR,

Anorgasmia in women is a recognised side-effect of clomipramine (Anafranil data sheet) and has been reported with imipramine (Sovner, 1983). We report two cases of anorgasmia, one induced by clomipramine, the second by imipramine, which resolved with cyproheptadine. A third patient who had imipramine-induced anorgasmia failed to respond to this treatment.

Case 1: Mrs E. T., aged 36 years was prescribed clomipramine for depression. The dose was started at 25 mg nocte and increased to 75 mg. Within two weeks of starting this treatment she experienced anorgasmia. She could become sexually aroused but was unable to achieve orgasm either during intercourse or by masturbation. This situation had persisted for three months during which time clomipramine 75 mg nocte was continued. A reduction to 50 mg nocte did not improve her sexual functioning. She continued to take clomipramine 50 mg nocte and was given a supply of cyproheptadine 4 mg tablets with instructions to take one tablet ninety minutes before anticipated sexual activity. If after trying this on four occasions she was still anorgasmic she was to progressively increase the dose. The first time that she took 8 mg cyproheptadine she experienced orgasm in response to masturbation. So long as she takes cyproheptadine 8 mg before sexual activity she is orgasmic. She failed to achieve orgasm after taking placebo tablets which she was told were cyproheptadine 8 mg.

Case 2: Miss A. C., aged 22 became depressed after a broken love affair. She was treated with imipramine, starting with 25 mg nocte and increasing to a total daily dose of 100 mg. Within a week of increasing the dose to 75 mg she experienced anorgasmia during masturbation, her only form of sexual outlet. She had previously been multiorgasmic and had regularly masturbated 3–4 times a week. She continued to take imipramine 100 mg daily and was given a supply of placebo tablets. She was told to take these tablets ninety minutes before masturbation, increasing the dose from one to four tablets. This did not resolve the anorgasmia. She was then started on cyproheptadine and became orgasmic when she took 12 mg before masturbation (the placebo tablets did not match the active tablets).

Case 3: Mrs W. M., aged 28 had been taking imipramine 150 mg daily for depression for six months. During this time she consistently failed to achieve orgasm. Before starting this treatment she was coitally orgasmic on about 50% of occasions. She was given placebo tablets and then cyproheptadine tablets as in Case 2. Neither the placebo nor cyproheptadine 8 mg resolved the anorgasmia. Drowsiness induced by the cyproheptadine prevented further increments in dose. Desipramine 100 mg daily was substituted for the imipramine but this change of treatment did not resolve the anorgasmia. She was then weaned off anti-depressants and again became orgasmic.

The physiology and pharmacology of sexual function are poorly understood. Animal studies have

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