await resolution, the fact remains that the drug is rapidly eliminated and the duration of any side effects such as vomiting and dizziness is likely to be limited in the newborn infant. This has recently been confirmed in a more extensive study on the utility of meptazinol in labour pain (Nicholas & Robson, to be published).

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FAVOURABLE EFFECTS OF YOHIMBINE ON CLOMIPRAMINE-INDUCED ORTHOSTATIC HYPOTENSION: A DOUBLE-BLIND STUDY

Tricyclic induced orthostatic hypotension is a frequent side effect often more severe than many clinicians seem to believe (Glassman *et al.*, 1979).

In a preliminary open study of 11 patients (Des Lauriers *et al.*, 1979) we showed that yohimbine, a presynaptic α-noradrenergic receptor blocking agent, had favourable effects on orthostatic hypotension induced by clomipramine, a tricyclic antidepressant. We believe the hypotension seen with clomipramine is probably the result of the blockade of α-adrenergic post-synaptic receptors. Our initial findings suggested a favourable effect:

(a) on blood pressure figures upon standing: the decrease in systolic blood pressure was 32 mmHg before treatment and 11 mmHg after 1 week treatment.

(b) on clinical symptoms (mainly dizziness) which disappeared in 10 out of 11 subjects.

A double-blind controlled trial was undertaken in order to confirm these findings.

All subjects were hospitalized, depressed patients presenting with clomipramine-induced orthostatic hypotension after at least 5 days of treatment. Patients were included in the trial if the decrease in

Table 1 Decrease of systolic BP (mmHg ± s.d.) measured at days 0–3 and 7 of treatment, after change to upright position in 12 subjects presenting clomipramine induced orthostatic hypotension.

	After 30 s			*After 2 min*		
	Day			*Day*		
	0	*3*	*7*	*0*	*3*	*7*
Yohimbine	36 ±11.7	21* ±7.3	16,5* ±6.2	35 ±12.2	13,5* ±8	10,5* ±5
Placebo	42 ±7.2	35 ±9.1	41 ±7.9	37 ±5	26,5 ±6.9	34 ±12

The difference between placebo ($n = 6$ patients) and yohimbine ($n = 6$ patients) is significant at * : $P < 0.01$.

systolic blood pressure was greater 20 mmHg upon standing upright.

Blood pressure was always recorded by the same observer with the same apparatus (standard mercury sphygomomanometer). Measurements were made in the morning between 09.00 h and 10.00 h at days 0–3 and 7 of treatment. Systolic blood pressure was studied in the recumbent patient after a period of rest, then 30 s and 2 min after the patients stood up. The recumbent and standing heart rates (after 2 min) were also measured.

Diastolic blood pressure was not measured in most patients presenting with orthostatic hypotension because we believe this measure is either inaccurate or difficult.

The presence of dizziness and dryness of the mouth was rated 0 = none, 1 = present but mild, 2 = severe and causing discomfort, 3 = incapacitating.

Statistical analysis were made using Student's *t*-test on the difference between the scores before and after treatment or Student's paired *t*-test.

Treatments were as follows:

Clomipramine had been administered for at least 5 days at a dose of 150 mg/day for at least 2 days. It was continued unchanged during the whole trial.
Either yohimbine (1 tablet = 2 mg) or placebo = 6 tablets per day was given.

Treatment allocation was randomized and adjusted every 4 patients.

Benzodiazepines and lithium were allowed. We hoped to study 24 patients (12 placebo, 12 yohimbine) with an intermediate analysis when 12 patients had been studied. After examination of the results in the first 12 patients however, we decided to discontinue the study.

Table 1 shows the decrease of orthostatic systolic blood pressure before and after treatment. Yohimbine compared with placebo significantly improves the blood pressure fall beginning on the third day of treatment both at 30 s and 2 min. Only one patient out of six did not improve in the yohimbine group, only one had spontaneous amelioration in the placebo group.

Figure 1 shows the results for each patient 2 minutes after standing measured after one week of treatment.

There is an increase in the recumbent systolic blood pressure (Table 2) in the yohimbine group, and no change in the placebo group. However, initial blood pressure figures were higher in the placebo group and patient's blood pressures before treatment were not known.

Only five patients in each group had clinical symptoms (Table 3). Dizziness was markedly and significantly improved in all patients. Results are far less clear as regards dryness of the mouth.

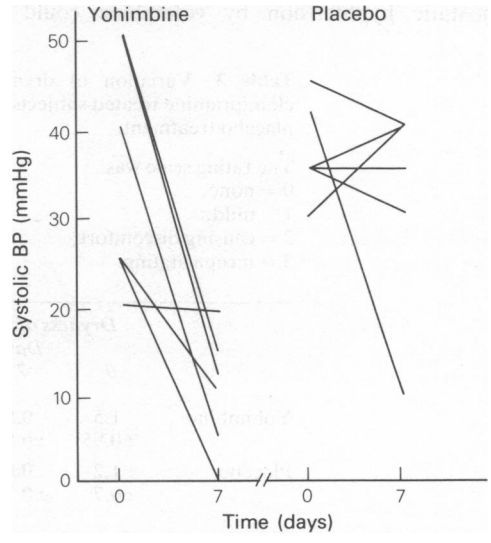

Figure 1 Change in systolic BP 2 min after assuming orthostatic position before treatment and after 7 days treatment.

Table 2 Recumbent systolic BP (mmHg ± s.d.) after a period of rest in 12 subjects presenting with clomipramine induced orthostatic hypotension recorded at days 0–3 and 7 of treatment.

	Days			
	0	*3*	*7*	*0–7*
Yohimbine	102 ±14.3	119 ±13.3	122 ±20.9	+20* ±9.5
Placebo	118 ±4.7	118 ±10.2	118 ±22	0 ±17

* $P < 0.05$

The results of the heart rate measures showed no difference between the two groups. However it can be noted that in all cases a compensatory tachycardia was present.

Despite the small number of patients this controlled double-blind study gives evidence of yohimbine's therapeutic efficacy in the treatment of clomipramine-induced orthostatic hypotension, both on blood pressure figures and clinical parameters. The efficacy of yohimbine appears to be superior to the one demonstrated with substances currently used for that indication.

The mechanism of clomipramine-induced orthostatic hypotension is not clearly established. It might be the result of an increase in central noradrenergic activity due to inhibition of noradrenaline reuptake by clomipramine. Blood pressure is regulated by α_2-type noradrenergic receptors which are stimulated by clonidine and blocked by yohimbine (Langer, 1977). Thus, the antagonism of clomipramine-induced orthostatic hypotension by yohimbine could be related to the blockade of central α_2-noradrenergic receptors.

Another hypothesis is that tricyclic antidepressants besides inhibiting recuptake, interact directly with various receptors: muscarinic, adrenergic, serotoninergic and histaminergic (U'Pritchard *et al.*, 1978). The blockade of α_1-noradrenergic receptors could explain orthostatic hypotension. In this case, yohimbine would antagonize this effect by blocking α_2-presynaptic receptors (Langer, 1977).

Noradrenaline release is more important for blood pressure control when the vasomotor system is stimulated, since the amount of noradrenaline released by each action potential is increased when the presynaptic receptor is blocked. Therefore this increase takes place during the vasoconstriction reflex induced by orthostatic position and is antagonized when it is most necessary during clomipramine blockade of α-post-synaptic receptors.

However, the rise in recumbent blood pressure deserves particular attention, as two hypotheses can be raised:

(a) defective venous return during clomipramine treatment in recumbent patients; however such hypotension is rarely reported with tricyclics.

(b) hypertensive effect of yohimbine which, though moderate would indicate the need for monitoring and caution particularly in patients with hypertension.

One of the classical contra-indications of high doses of yohimbine, resulting from animal studies, is hypotension. This hypotension is due to the blockade of α-post-synaptic receptors by yohimbine, which occurs only with high doses. At low doses, yohimbine only blocks α-pre-synaptic

Table 3 Variation of dryness of the mouth and dizziness in 12 clomipramine treated subjects rated before and after 1 week yohimbine *v* placebo treatment.

The rating scale was:
0 = none;
1 = mild;
2 = causing discomfort;
3 = incapacitating.

	Dryness of the mouth *Days*			*Dizziness* *Days*		
	0	*7*	*0–7*	*0*	*7*	*0–7*
Yohimbine	1.5 ±0.95	0.5 ±0.5	−1 ±0.8	2 ±1	0.35 ±0.47	−1.65* ±0.95
Placebo	1.2 ±0.7	0.85 ±0.7	−0.35 ±0.47	1.5 ±0.95	1.15 ±1	−0.35 ±0.75

Note: only 5 patients in each group had clinical symptoms initially. If calculations are made on that group of patients the decrease in dryness of the mouth nears significance ($t = 2.00$).
* $P < 0.05$.

receptors (Langer, 1977), thus increasing noradrenaline release which can account for a hypertensive effect.

It seems logical to believe that with the dose levels used in the present study yohimbine should block the vasomotor regulation mechanism at a central level as well. This would have two consequences:

(1) the possibility of an antidepressant effect of yohimbine itself since a therapeutic role of noradrenergic function stimulation in the treatment of depression has been described (Puech, Lecrubier & Simon, 1979).
(2) Synergistic action with tricyclic antidepressants, if these drugs increase the amount of transmitter present in the synaptic cleft by blocking its reuptake. The neurotransmitter decreases its own release by stimulating the pre-synaptic receptor. Blocking this feedback mechanism should allow a quicker and more stable effect of tricyclics.

Preliminary studies to test these hypotheses are currently underway and seem encouraging.

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EFFECT OF PROPRANOLOL LA ON AMBULATORY BLOOD PRESSURE

We wish to comment on the conclusions drawn from the study of the effects of propranolol LA on ambulatory blood pressure recently reported by Mann *et al.* (1980). Of the twelve previously untreated Group I patients, only seven were subsequently restudied; consequently, these represent a highly selected sub-group. In the summary, it is stated that 'smooth control of blood pressure and heart rate occurred throughout 24 h'. Unfortunately, the results did not demonstrate such a reduction in blood pressure: of the 48 possible comparisons of hourly mean systolic and diastolic pressure, a significant difference was observed in only 18; in none of the comparisons between midnight and midday was a significant difference demonstrated. No substantial conclusions may be drawn from the Group II patients in whom conventional propranolol was changed to propranolol LA, since four of the six patients were taking other hypotensive drugs (diuretics and hydrallazine); no evidence was presented of a hypotensive effect which could have been attributed to propranolol alone.

Finally, we would draw your attention to a typographical error: Millar Craig *et al.* (1978) investigated the effects of oxprenolol in 20, not 200, patients.

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