## Phentermine and other monoamine-oxidase inhibitors may increase plasma serotonin when given with fenfluramines

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Phentermine has been used in the USA to treat obesity since at least 1961 and was widely used after 1992 in combination with fenfluramine. A study in 1997 suggested that this combination could be associated with heart-valve disease similar to that seen in the carcinoid syndrome or in patients who had taken ergotamine, as well as with pulmonary hypertension, previously described.[1] It was suggested that these findings, were due to an increase in circulating serotonin. Subsequently, the US Food and Drug Administration found heart-valve lesions among patients taking a fenfluramine without phentermine.

Given the paucity of data on phentermine's actions, we determined whether phentermine could modify the metabolism of other monoamines besides the norepinephrine released from sympathetic neurons. In rats, phentermine, like *d*-amphetamine, releases dopamine into brain synapses.[2] We tested the ability of a low dose (15 mg by mouth) to affect plasma dopamine in human beings. Nine young, non-obese male volunteers gave blood just before, and 1, 2, or 4 h after receiving the drug. Plasma dopamine concentrations, assayed by radioimmunoassay[3], rose with phentermine ($p<0·05$; ANOVA; Wilcoxon's test); however a greater increase was noted in serotin levels within the blood platelets as assayed by ELISA and confirmed by high performance liquid chromatography ($r=0·496$; $p<0·001$). The increase in platelet serotonin could reflect increased release of serotonin from enterochromaffin cells, or inhibition of its metabolism by monoamine oxidase (MAO). That the increase resulted from MAO inhibition and not from increased serotonin release was shown by the finding that plasma serotonin concentration fell slightly.

That phentermine inhibits the MAO which catabolises serotonin was well known in the early 1970s,[4] but apparently this information never made its way onto the drug's label. There is evidence that free plasma serotonin can damage vascular tissue[5] and that its concentration is normally kept low by the action of the two high-capacity systems that remove it from the circulation—uptake into platelets and MAO. If the fenfluramine and phentermine regimen did produce pulmonary hypertension and cardiac valve lesions then they might have been obviated had the phetermine label within the US mentioned that the drug is an MAO inhibitor. Such a mention would also warn physicians against combining phentermine with fluoxetine, flenfluramine, or other SSRIs.

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## MRI of entorhinal cortex in mild Alzheimer's disease

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The entorhinal cortex (EC) is important in recent memory performance[1] and a consistent site of neuronal pathology and volume loss in the earliest stages of Alzheimer's disease.[2,3] Magnetic resonance measurements of the EC size may, therefore, be of potential use for in-vivo diagnosis of early Alzheimer's disease. The histological boundaries of the EC are not easily visible on magnetic resonance scans.[4] Therefore, with histological sections taken from brains of patients with necropsy-confirmed Alzheimer's disease and from normal controls, we validated a method for measurement of EC size that relies on gyral and sulcal landmarks visible on magnetic resonance imaging. Subsequently, with magnetic resonance imaging we applied the validated landmark method in vivo to separate patients with mild Alzheimer's disease from age-matched controls free of the disease. All participants and, if appropriate the next of kin, gave informed consent for the research.

In the validation study we used coronal cresyl violet-stained histological sections spaced every 3 mm that covered the entire anterior-posterior extent of the EC. Three measurements were made at ×28 magnification, on all slices containing EC in 16 patients with moderate to severe Alzheimer's disease (mean age 81·2 [SD 6·3] years) and for four normal elderly patients (76·9 [4·8] years). First, we found the histological boundaries of the EC and calculated the EC volume. Second, the distance on the pial surface of the brain between the most superior (medial) and most inferior (lateral) EC boundaries was defined and called the histological length of the EC. Third, using sulci and gyri, which are reliable landmarks on magnetic resonance imaging, we measured EC length (landmark EC length, figure). Examination of the tissue, demarcated with the landmark length method, showed that almost the entire entorhinal cortex and a portion of the perirhinal cortex were included. As a summary measure, we estimated the surface area of the EC by adding the length measurements across slices and multiplying by the slice thickness.

With necropsy samples from the total group of patients with Alzheimer's disease and controls (n=20), the volume of the EC was associated with histological ($r=0·94$, $p<0·001$) and landmark EC surface areas ($r=0·91$, $p<0·001$). The landmark and histological surface areas were associated with each other ($r=0·83$, $p<0·001$). For the Alzheimer's disease group (n=16), EC volume was associated with the landmark surface area ($r=0·70$, $p<0·002$). The mean differences between groups were comparable for the three EC measurements. The mean volume of the EC was 61% less in the Alzheimer's disease group than in the normal group (410·6 [104·0] *vs* 1041·1 [73·4] $mm^3$, $p<0·001$); the histological EC surface area was decreased by 49% (152·1 [23·4] *vs* 300·3 [38·7] $mm^2$, $p<0·001$); and the landmark EC surface area was decreased by 45% (232·2 [38·7] *vs* 424 [94·2] $mm^2$, $p<0·001$).

In vivo, we obtained magnetic resonance scans for eight normal controls and eight patients with very mild to mild