could not be monitored. Even these patients could have been treated as outpatients if adequate professional care had been available at home. No serious complications were noted in patients treated in an outpatient setting. Another 9% of our patients presented in the emergency room and were already being treated for deep vein thrombosis suspected on clinical grounds alone. They were admitted until ultrasound examination could be performed.

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Contributors: TS and SMS had the original idea for the study, recruited a large number of patients, created the trial database, analysed the data, and wrote the paper. BS conducted statistical analysis and recruited patients. UH advised on data collection and analysed the data. JB recruited patients for the study. HES revised the final version of the manuscript and is the guarantor of the paper. All authors approved the final version of the paper.

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Drug points

Pseudophaeochromocytoma syndrome associated with clozapine

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Clozapine (Clozaril, Novartis), a tricyclic dibenzodiazepine derivative, has an established role in the treatment of refractory schizophrenia. In the United Kingdom the drug may only be prescribed by consultant psychiatrists registered with the Clozaril Patient Monitoring Service; this reflects the serious adverse effect profile of the drug, which includes agranulocytosis. Paradoxical hypertension with increased concentrations of urinary catecholamines has also been reported, albeit rarely and in association with other antipsychotic treatment.[1]

We describe four patients with a pseudophaeochromocytoma syndrome associated with clozapine. All had serious refractory psychiatric disturbances. Case 2 presented to a cardiology clinic with hypertension for which she was receiving bendrofluazide 2.5 mg daily, and case 3 was referred to a diabetes clinic with type 2 diabetes (treated with metformin 500 mg twice daily) and dyslipidaemia. Case 4 was initially referred to a renal clinic with hypertension. Profuse sweating, hypertension, and obesity were common to all the patients; intermittent tachycardia was noted in cases 1 to 3 (table). Renal and hepatic function were normal in all the patients, and there was no evidence of alternative causes of secondary hypertension. The interval between the start of clozapine treatment and the development of the clinical features varied (table), being evident within one week in case 1. Urinary catecholamine concentrations, measured in 24 hour collections during clozapine treatment, were increased in all four patients (table). To exclude the possibility of phaeochromocytoma, case 1 underwent computed tomography and cases 3 and 4 underwent isotopic imaging.[2] In cases 1 and 2, urinary catecholamine concentrations normalised, and clinical features improved or resolved after withdrawal of the drug; these patients also lost several kilograms in body weight. Clozapine was continued at a lower dose in case 3 as the supervising psychiatrist advised against its withdrawal. Treatment was also continued in case 4 because his blood pressure settled spontaneously.

The neuropharmacological actions of clozapine are complex and include affinity for 5-HT_2 receptors and for adrenergic receptors in vitro.[3] Clozapine has been reported to cause increases in plasma noradrenaline concentrations, a postulated mechanism being the inhibition of resynaptic reuptake mediated by α_2 adrenergic receptors.[4] Sulpiride, which blocks presynaptic α_2 adrenoreceptors, may have contributed to the clinical features in cases 2 and 4.[5]

We contacted the manufacturer, Novartis, and the Committee on Safety of Medicines about this adverse event.

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Clinical details of patients and catecholamine concentrations

Case No	Age (years)	Sex	Body mass index (kg/m²)	Clozapine dose (mg/day) and duration of treatment*	Other drugs	Heart rate (beats/min)	Blood pressure (mm Hg)	24 hour urinary catecholamine concentration (µmol) (reference range)
1	27	Male	31	400 for 2 months	Fluoxetine 20 mg daily	110	170/120	Noradrenaline 1.68 (<0.59), vanillylmandelic acid 54 (<35)
2	28	Female	38	700 for 12 months	Bendrofluazide 2.5 mg daily	104	143/112†	Noradrenaline 1.02 (0.08-0.45)
3	38	Male	40	900 for 18 months	Sulpiride 600 mg, venlafaxine 150 mg, and metformin 500 mg twice daily	130	156/100	Noradrenaline 0.53 (0.07-0.48), normetadrenaline 4.3 (0-3.00)
4	22	Male	30	600 for 3 months	Sulpiride 200 mg daily and paroxetine 50 mg daily	NA	180/120	Noradrenaline 0.90 (0.07-0.48), normetadrenaline 4.6 (0-3.00)

NA=not available. *Before measurement of 24 hour urinary catecholamine concentration. †Average during ambulatory monitoring.