# Serotonin syndrome: potentially fatal but difficult to recognize

DEPRESSION is common. A general practitioner with an average list size can expect approximately 40 patients to meet ICD-10 criteria for depressive disorder at any one time.[1] Depression causes misery to the individual, a strain on families, colleagues and friends, and countless lost working days. Individuals with depression are at high risk of suicide and physical illness.

Antidepressants are effective in reducing the psychological and physical symptoms of depression, with a number needed to treat of around three (far better than many interventions for physical illnesses). When combined with psychological and social approaches to management, antidepressants have a powerful treatment effect. More recently, the role of certain antidepressants in treating panic disorder, eating disorders, and obsessive-compulsive disorder has been recognized.

Since the introduction of fluoxetine 12 years ago, the selective serotonin reuptake inhibitors (SSRIs) and allied compounds have now overtaken traditional tricyclic antidepressants (TCAs) in terms of market share. Although safer in overdose and with less anticholinergic and antiadrenergic activity, evidence for better tolerability of SSRIs is less robust, and the safety of SSRIs and related compounds may have been overestimated. Many are potent enzyme inhibitors with potential for significant interactions with other drugs. Dystonias, akathisia, and discontinuation syndromes have all been reported. In this *Journal*, Mackay *et al* raise awareness of another potentially serious adverse effect: serotonin syndrome (SS).[2]

Serotonin syndrome was first described in animals in the early 1960s. The use of the serotonin precursor, L-Tryptophan, led to case reports of toxicity in humans and, since the late 1960s, many drugs and drug combinations have been implicated. Combinations of SSRIs with drugs that act as serotonin precursors or agonists such as LSD, lithium, L-DOPA, and buspirone are known to cause the syndrome; as is Ecstasy (MDMA), which stimulates serotonin release. Cocaine and monoamine oxidase inhibitors are non-specific inhibitors of serotonin metabolism. There are also case reports describing SS with Tramadol and pethidine, which also inhibit serotonin reuptake at the synapse.

Serotonin syndrome was first fully described in humans by Sternbach,[3] who defined the diagnostic criteria outlined in the article by Mackay *et al*.[2] In his review of 38 case reports, Sternbach reported the most common clinical features to be restlessness (45%), confusion (42%), myoclonus (34%), hyperreflexia (29%), and sweating, shivering, and tremor (26% each). Nearly all reported cases occurred in patients taking a combination of antidepressants and other psychotropic agents, although SS has been described in monotherapy with SSRIs in susceptible adults and in overdose of single SSRIs in adults and children. Serotonin syndrome has been reported in patients with a wide range of diagnoses: bipolar affective disorder, unipolar depression, obsessive compulsive disorder, Parkinson's disease, and tuberculosis (anti-tubercular drugs such as isoniazid are serotonergic).

Serotonin syndrome is easily missed because of the protean ways the syndrome may manifest and the lack of definitive clinical features. There are no core features present in all (or nearly all) cases. Patients and clinicians alike may dismiss symptoms like tremor and diarrhoea as inconsequential or unrelated to their drug regimen; confusion and restlessness may be attributed to the underlying mental state. The difference between full-blown SS and the effects of SSRIs alone lies in the clustering of signs and the severity and duration of the symptoms. Probably as a result of this difficulty in recognition, there have been no population-based studies on serotonin syndome. Consequently, little is known about the incidence of serotonin syndrome and the trend over time. The incidence is likely to be under-reported and it may be difficult to identify SS in its early stages.

Mild to moderate SS usually resolves completely when the drug is withdrawn in 24 to 72 hours. Rarely, SS can lead to rhabdomyolysis, myoglobinuria, renal or hepatic failure, disseminated intravascular coagulation, respiratory distress syndrome, and death. Laboratory tests show non-specific changes such as increased total white blood count and creatine phosphokinase and decreased bicarbonate levels. There are no diagnostic tests, although a scale is being developed.[4]

Because of the variable presentation, a number of differential diagnoses need to be excluded. Infections such as meningitis, septiceamia, and tetanus, and psychiatric conditions, such as catatonia or medication-related dystonia, need to be excluded. Overdose of lithium, cocaine, amphetamines, Ecstasy, aspirin, and anticholinergic drugs should be considered. The most common diagnostic confusion occurs in distinguishing SS from neuroleptic malignant syndrome, as many patients are prescribed neuroleptics and antidepressants together. Myoclonus is rare in neuroleptic malignant syndrome, which tends to present with more rigidity. It is possible that both syndromes are caused by a common neurotoxic mechanism.

The management of SS is mainly supportive. The precipitating medication should be removed and most cases will resolve without further intervention. Patients who are more severely affected may require antihypertensive drugs, anticonvulsants, or ventilation. No treatment studies have been carried out and case reports are the main source of possible therapies. Cooling and muscle relaxants may reduce muscle damage and thus rhabdomyolysis and renal failure. Benzodiazepines, dantrolene, propanolol, and cyproheptadine have been reported as useful in some cases. The main aim, however, should be prevention of SS by avoiding polypharmacy with psychotropic agents.

Serotonin syndrome is probably a relatively rare event. At worse it may cause death but, even in mild cases, it may cause distressing symptoms and significantly impair future compliance with antidepressants. Awareness of the clinical features and risk factors will aid early identification and may prevent a more serious outcome.

ELIZABETH SAMPSON

*Specialist registrar, St Charles Hospital, London*

JAMES P WARNER

*Senior lecturer, Imperial College School of Medicine*

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**Address for correspondence**

Dr Warner, Department of Old Age Psychiatry, Imperial College School of Medicine, St Charles Hospital, Exmoor Street, London W10 6DZ. E-mail: j.warner@ic.ac.uk

# The future for non-principal general practitioners: Lost doctors — lost to whom?

RECRUITMENT and retention of general practitioner (GP) principals is at crisis in many parts of the country,[1,2] particularly in areas of deprivation.[3] The introduction of primary care groups (PCGs) on 1 April this year has increased demands on existing principals even more as they are taken away from clinical duties to do administrative work in the PCGs. Many practices have therefore become increasingly reliant on non-principals, and principals need to know that the non-principals in their practices are providing a 'quality' service.[4] This should be a PCG clinical governance responsibility.

Non-principals are a heterogeneous group of vocationally-trained GPs including assistants, retainers, and locums. They are a large group representing at least a tenth of the general practice workforce; 60% to 75% of them are women,[5-7] and more than half are employed for fewer than 25 hours per week.[5] Non-principals are ignored in official reports and statistics: locums, for example, are not mentioned in either the Government Statistical Service Review[8] or the Medical Workforce Standing Advisory Committee Third Report.[9] All GPs, whether principals or non-principals require the same training and qualifications to practise, yet non-principals are discriminated against in terms of income, employment conditions, access to education and information, and status within the profession. Non-principals will have to be revalidated just like principals.

So why do doctors work as non-principals when they could apply for posts as principals? The 'Lost doctors' project[5] found that many were working as non-principals *by choice* for three main reasons. First, they wished to work part-time to balance GP work with domestic and family responsibilities, other paid work, or interests. Secondly, while committed to fulfilling a clinical role, they wanted to avoid the inflexible working hours, being on-call, or the managerial responsibilities of a traditional principal role. Thirdly, they felt unable to make a long-term commitment to a practice because of family mobility. While further training may encourage some non-principals to become principals,[10] it may be unrealistic to expect that most non-principals can be attracted into partnership. This is because they seek a lifestyle that balances their GP work with other interests.

The GP recruitment crisis could perhaps be more effectively addressed, not by attempting to attract more doctors into partnership, but by maximizing the potential contribution of the existing pool of highly-trained, committed GP non-principals, in whose training large sums have been invested. This could be achieved in a number of ways.

First, a wider availability of salaried posts is needed, with contractual arrangements that provide for holiday, sickness, maternity and study leave, superannuation, medical defence insurance, and financial support towards education and training. The new GP Retainer Scheme[11] has introduced changes that go some way to meeting this need, by increasing the number of sessions that can be worked to up to four per week, and by introducing entitlements to study leave, sick leave, and maternity leave. While the new retainer scheme appears to be popular anecdotally, there has been a disappointingly low uptake of additional National Health Service (NHS) Executive funding to support the setting up of salaried GP posts.[12,13] This is probably because of limited, insecure, and short-term funding.

Secondly, non-principals need representation at national and local level. The General Practice Committee (GPC) established a non-principal subcommittee two years ago, and two subcommittee members sit on the GPC. Over the past year they have negotiated the new retainer scheme, new rates of pay for employed non-principals, and produced a draft contract for retainers.[14] The GPC have recently recommended to Local Medical Committees (LMCs) that they allow non-principals to pay a small voluntary levy. This will entitle them to membership of LMCs and is a further step towards equity for non-principals in the medico-political field.

Thirdly, a change in the culture of general practice is needed in which doctors working as non-principals are valued equally with their principal colleagues as providers of clinical care. The National Association of Non Principals (NANP), a voluntary organization run mainly by locums, has acted as an effective lobby for the rights of non-principals. The NANP has a code of good practice (available from the website: www.nanp.org.uk) endorsed by the Royal College of General Practitioners that aims to foster good relationships between all those working in general practice and to promote high standards of medical care. Practices and their staff have a responsibility to help non-principals deliver a high standard of care by supporting them, as they do principals. This can be achieved by being well organized, with appropriately equipped consulting rooms, and by providing up-to-date information about the practice and locality. The NANP has produced a model 'Practice Induction Pack' for provision of standardized information about practice meetings, policies, drug reps, computer systems, and communications. Practical steps should be taken to ensure that non-principals are able and encouraged to participate in practice team meetings and educational activities. Principals may feel that non-principals are 'cherry-picking' the most popular work of a GP (surgeries) and rejecting the less popular aspects of the job (administrative tasks, paperwork, out-of-hours work, etc.). Principals need to remember the ways in which non-principals are discriminated against, as mentioned above, and reflect that good quality clinical care to the patient will result if the non-principal's task is facilitated. The GP recruitment and retention crisis has had more impact in certain settings (inner cities, deprived areas) and geographical areas. Flexible and imaginative policies will be needed to attract more doctors into these areas. An increase in the employment of salaried GP non-principals could help to alleviate these GP workforce problems and maintain primary care services for those populations most in need.

Fourthly, a local and national register of GP non-principals should be set up. This would have benefits for the Department of Health by providing a means of identifying and tracking these elusive ('lost to the NHS') doctors, enabling them to be included in workforce planning. The NANP and the GPC have both established national databases, but neither is a definitive, recognized list with specific, tangible benefits for registering doctors. The two groups need to work together for the benefit of all non-principals. It would be of advantage to non-principals by enabling equity of access to both local information on guidelines and policies, hospitals, voluntary agencies and social services, educational and job opportunities, as well as to national mailings. The NANP has recently clarified the mystery regarding the poor supply of British National Formularies (BNFs) to non-principals, which has been a great source of grievance, as, without an up-to-date BNF, how can any doctor provide the best clinical care.[3] The NHS Executive has confirmed that all GPs should receive a free BNF twice a year from their local health authority. The main obstacle to supply is the 'conspiracy of ignorance' that surrounds the whereabouts of non-principals. The NANP will supply a pre-formatted letter that can be passed to health authorities, reminding them of their requirement to provide free BNFs to non-principals. In a quality service, non-principals need access to information about their prescribing in the same way as principals. Changes in prescribing regulations could allow personal prescription pads to be available for non-principals and PACT data could then be produced.

Lastly, all doctors, whether practising or not, should participate in continuing professional development (CPD).[15] The educational needs of non-principals have been discussed in a recent editorial,[16] and, in February, the GPC hosted a national conference on the subject. It is in the interests of both the profession and patients to ensure that non-principals have equitable access to the same quality CPD available to principals. Specific mechanisms for funding the professional development of GP non-principals need to be identified. The GPC acknowledges that a process of life-long learning should be available for all GPs,[17] but acknowledges that clarification will be required that all GP non-principals will be able to access it.

In conclusion, much remains to be done to ensure a future for GP non-principals in which their skilled contribution to servicing the general practice workload is fully recognized and rewarded. Non-principals are voting with their feet for a more sensible workload and work pattern in general practice. General practice needs to move with the times and offer flexible, family-friendly employment opportunities for these well-qualified and committed doctors.

JUDY SHAKESPEARE

*General practitioner, GP tutor for Oxfordshire, and chair of the 'Lost doctors' project steering group, Oxford*

JULIE EVANS

*Research officer, UK Medical Careers Research Group (formerly of the Public Health Resource Unit), Institute of Health Sciences, Oxford.*

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### Address for correspondence

Dr Judy Shakespeare, Summertown Health Centre, 160 Banbury Road, Oxford OX2 7BS.