However, it is difficult to fathom why routine therapeutic drug monitoring (TDM) is still not considered justifiable in clinical practice. Clozapine fulfils the criteria for TDM as it has a narrow therapeutic index, substantial inter-individual variations in daily dose and plasma concentration relationship, and complex metabolism. We suggest that TDM should start during the initial titration to determine the target dose, rather than being restricted to annual monitoring.

The *British National Formulary* mentions that the usual dose of clozapine is between 200 and 450 mg, and the maximum is 900 mg per day. The Summary of Product Characteristics of clozapine further suggests that once patients have achieved maximum therapeutic benefit, many can be maintained effectively on lower doses. Owing to the significant inter-individual variations in bioavailability (up to 50 times), complex metabolism and wide range of recommended oral dosages, in clinical practice the dosage of clozapine is usually guided by nomograms. These nomograms were developed many years ago to predict plasma levels of clozapine taking into account only two covariates, gender and smoking status. These nomograms' predictive values are associated with wide confidence intervals.[2] Hence, it is not surprising that the authors found significant variations in plasma clozapine levels (<0.1 to >1 mg/L). We are assuming that most patients were receiving the recommended dosages of clozapine.

Clozapine is associated with many significant adverse effects, and these are the most commonly cited reasons for discontinuation during the initial phase of treatment.[3] The most important adverse effects from the patients' perspectives are sedation, hypersalivation and constipation, and these are probably dose-related adverse effects.[3,4] Moreover, clozapine is the only evidence-based treatment for patients with treatment-resistant schizophrenia, and most patients will stay on it on a long-term basis; hence it is important that patients should be treated with the minimum effective dose.

The recommended plasma clozapine levels of 0.35–0.60 mg/L are for the management of active psychotic symptoms. The recommended plasma levels for maintenance treatment might be lower than the above range.[4]

The authors have highlighted concerns about high clozapine levels and their potential association with high mortality. Lower clozapine levels are also of concern, especially if a patient has partially responded to clozapine. Hence, there is now increasing support for the view that TDM should be used during the initial phase of clozapine treatment to achieve minimum therapeutic levels.[4] Subsequently, dosages can be optimised, based on the response and side-effects burden. At present, this is difficult as clozapine assays are done by selected centres in the UK, and it can take a few days to weeks to get the results. Even then, it will be prudent to obtain plasma clozapine levels soon after the titration. In the future, point-of-care testing for clozapine might make it easier to titrate the dose to achieve the minimum therapeutic level.[5]

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## Declaration of interest

S.G. has received honorariums for lectures from Viatris, one of the marketing authorisation holders of clozapine.

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## Author's Reply. RE: Routine clozapine assay monitoring to improve the management of treatment-resistant schizophrenia

I would very much like to thank Sumeet Gupta and Liyana Nur Mohamad for their supporting comments. Hopefully, there are many more like-minded clinicians who would also wish to see further developments in this area. The potential benefits to all involved are truly enormous.

Clozapine is a unique and usually efficacious treatment for a significant group of the mental health population with treatment-resistant schizophrenia (TRS). However, in my experience, it would seem that only a fraction of the people who fulfil the criteria for a diagnosis of TRS are actually considered for clozapine treatment. The reasoning for this under-treatment is multifactored, but the general theme of various safety concerns with regard to the longer-term management of clozapine is invariably foremost in clinicians minds.

The robust moves we have made to ensure that clozapine therapeutic drug monitoring is a significant facet of every patients care plan have allowed us to: (a) identify previously unknown clinical risk and manage it carefully; (b) build a data-set of results for each patient, which is a helpful tool for overall clinical assessment; (c) improve clinical outcomes and reduce mortality; (d) improve the confidence of clinicians, which has allowed them to be more agile with their prescribing of clozapine; and (e) support clinicians to feel encouraged to consider more patients for clozapine, which is reflected in our above-average recruitment of patients for treatment.



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I agree that the current provision for assay testing across the UK could be improved. However, the necessary laboratory technology has become more available over time, and I would encourage clinicians to develop dialogue with both national and local pathology laboratories to explore the potential service development.

Clozapine has been the gold standard treatment for TRS for many years, and yet it is still mostly underutilised. We need to address this serious shortfall in service provision.

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## Declaration of interest

None

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# Obituary

## Raghu Gaind, FRCP, FRCPsych, DPM

Formerly Physician in Psychological Medicine, Guy's Hospital, London, UK

Raghu Gaind, who died on 7 September 2021 aged 86, was a man of immense energy, and had an extraordinarily diverse career. After working as an NHS consultant in psychiatry, he took early retirement at 50 and then ran a large private practice in London. He set up two private nursing homes (Suttons Manor psychiatric clinic in Romford, Essex, and a clinic for the elderly mentally infirm in Beckenham, Kent). He organised numerous successful courses for psychiatrists in the UK and abroad. He served as an examiner in psychiatry in numerous countries throughout the world. For 30 years he edited a series of books titled *Current Themes in Psychiatry*, which over five editions summarised contemporary thinking on the subject. He was active in social psychiatry, editing the *International Journal of Social Psychiatry* for 5 years. For some years he was chair of the now closed Institute of Social Psychiatry, and was elected Secretary General of the World Association for Social Psychiatry in 1985, serving in this capacity until 1991.

Most notable, however, were his philanthropic activities, undertaken particularly in India. He was Chairman of the Arpana Charitable Trust (UK), which helped finance a 125-bed hospital in Chandigarh, India, with community outreach services concentrating on the empowerment of women in rural communities among the poorest of the poor. With Prince Charles (now King Charles III) as its royal patron, this charity has raised funds totalling around £4.5 million over 20 years. It has carried out pioneering work in Delhi, where it was involved in the resettlement of some 30 000 street dwellers and inhabitants of shanty towns. Raghu was patron of a number of other Indian charities, including the Maitreey Mission, which is involved in the treatment and rehabilitation of people with leprosy living in colonies in and around Delhi. He also helped to create facilities for young children from a leprosy colony (Ramakrishna Puram, in Delhi). In 1992 he was awarded the title Distinguished Citizen of India by the Indian Government for his social contributions. In later years he publicised the plight of Tibetan refugees, particularly those in the Chamba District.

Raghu was born in Jammu, Kashmir, to Meher Chand Gaind, a barrister and Gian Devi. His family had served the maharajas for five generations, one member becoming Finance Minister to the state of Kashmir. As a child he learned Urdu and Farsi. He qualified from Amritsar Medical College in 1954 and shortly thereafter came to England to train in neurology at the National Hospital, Queen Square, and in psychiatry at the Maudsley Hospital and Institute of Psychiatry, London. While training and in his first years as a consultant, to support his large family (eventually he had six children), his ability for creative and prodigious work was exemplified by the fact that he worked as a general practitioner at weekends and as a police surgeon. He was regularly away from home from 8 a.m. to midnight. On one occasion he saw the same patient as a police surgeon in the emergency clinic at the Maudsley and as a registrar on the hospital ward. He was also actively involved at that time in what turned out to be highly influential research into drug medication in chronic schizophrenia.[1] He was appointed Physician in Psychological Medicine to Guy's Hospital in 1969 and Chairman of the Psychiatry Department in 1973, with beds in what was then St Olaves, Bermondsey and Bexley Hospitals.

His strong connection with the Middle East began in 1970, when he went with three other consultants to Saudi Arabia to help commission the King Faisal Specialist Hospital in Riyadh. He learned Arabic while he worked there for four and a half months. Subsequently, once a month he travelled to Saudi Arabia for a busy weekend seeing private patients. From 1970 to 1981 he was advisor in mental health to the Kingdom of Saudi Arabia. His global commitments rapidly extended. He was visiting professor and examiner to the University of Malta in 1980, the West Indies in 1981–1984, the University of California, Los Angeles (UCLA) in 1984–1985, the Punjab in 2003–2005 and Nairobi, Kenya, in 2007. He was awarded an Emeritus Professorship in Neuropsychiatry at Guru Ram Das College Amritsar, Punjab, in 2002.

As a result of his extraordinary capacity for hard work, his amazing charm and his ability to make warm, lasting friendships, combined with his considerable creative intelligence, Raghu did much to educate and entertain his colleagues. In 2011 he self-published a 700-page autobiography,[2] which makes interesting and amusing reading.

In 1959, he married June Beddoe, with whom he had six children. They divorced in 1987, and in 1989 he married Dr Susan Davenport, a consultant psychiatrist. She died from cancer after a short illness in August 2020. In 2000 Raghu self-diagnosed Parkinsonism and battled its slow progression over 20 years in a determined and courageous manner, meeting friends, playing bridge, going on cruises and travelling with Susan. He is survived by his first wife, his children