International Guidelines for the Algorithmic Treatment of Schizophrenia (INTEGRATE)

We read the Health Policy by Robert A McCutcheon and colleagues[1] with great interest and commend the authors for the focus on metabolic health from treatment initiation. We acknowledge the focus of INTEGRATE is primarily on pharmacological treatment and side-effect management, but we thought it essential to expand upon the recommendations around lifestyle interventions and implementation (eg, exercise, diet, and tobacco cessation).

In line with *The Lancet Psychiatry*'s Commission on protecting physical health in people with mental illness,[2] treatment guidelines should include simultaneous discussion of lifestyle interventions. This discussion is particularly relevant because people with schizophrenia are at elevated risk for a range of behavioural health risks, such as low physical activity, poor diet, and high rates of smoking, all of which contribute to the premature mortality in this population of around 20 years, largely due to cardiovascular disease.[2,3]

Although the provision of lifestyle advice was recommended throughout the guidelines, simply offering advice without specialist oversight to support these interventions is likely to fail. Unsupervised exercise or diet programmes, even when access to facilities and advice are provided, have been found to be ineffective for increasing physical activity or changing dietary patterns.[2] As such, exercise and diet interventions should be delivered by qualified professionals (ie, physiotherapists or dieticians) to improve adherence, while maximising physical and psychological benefits.[2,3] For smoking cessation, pharmacological interventions (ie, bupropion and varenicline) and non-pharmacological interventions (ie, the SCIMITAR+ trial) have proven effective in increasing smoking cessation. Although emphasis for lifestyle advice in INTEGRATE was placed on medications with a greater liability for metabolic adverse effects, such as olanzapine or clozapine, it is important to consider how all second-generation antipsychotics carry a metabolic burden, which can be minimised through concomitant provision of evidence-based lifestyle interventions.[3] Preventing conditions such as obesity and metabolic syndrome from arising is particularly important because it is considerably more efficient than attempting to reverse their long-term consequences.[2] Finally, we also note how recommendations towards providing lifestyle advice for only cardiometabolic side effects fails to take into account the results of multiple meta-analyses of randomised controlled trials in schizophrenia, which show the benefits of exercise interventions for physical and mental health outcomes, such as a reduction of psychiatric symptoms, improved cognition, and functional recovery.[4,5]

It is imperative that even pharmacologically based guidelines for the treatment of schizophrenia move beyond merely recommending lifestyle advice, towards actively calling for the provision of evidence-based lifestyle interventions. This shift can help to reduce physical health disparities while improving functional and mental health outcomes in this underserved patient population.

BS is supported by a National Institute for Health and Care Research (NIHR) Advanced Fellowship. BS is on the editorial board of *Physical Activity and Health*, *Ageing Research Reviews*, *Mental Health and Physical Activity*, *The Journal of Evidence Based Medicine*, and *The Brazilian Journal of Psychiatry*. BS has received honorarium from a co-edited book on exercise and mental illness (published by *Elsevier*), and unrelated advisory work from ASICS and FitXR. JF is supported by a UK Research and Innovation Future Leaders Fellowship (MR/Y033876/1) and the NIHR Manchester Biomedical Research Centre (NIHR203308). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. JF has provided consultancy and advisory services to Atheneum, Bayer, ParachuteBH, LLMental, Hedonia USA, and Arthur D Little, independent of this work. NM has received honoraria from Pfizer and Recordati, unrelated to the contents of this work. All other authors declare no competing interests.

*Nicholas Fabiano, David Puder, Joseph Firth, Nilufar Mossaheb, Brendon Stubbs
nfabi026@uottawa.ca

University of Ottawa, Department of Psychiatry, Ottawa, ON K1N 6N5, Canada (NF); Loma Linda University School of Medicine, Loma Linda, CA, USA (DP); Division of Psychology and Mental Health, University of Manchester, Manchester, UK (JF); Greater Manchester Mental Health NHS Foundation Trust, Manchester, UK (JF); Clinical Division of Social Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria (NM); Comprehensive Centre for Clinical Neurosciences and Mental Health, Medical University of Vienna, Austria (NM); Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK (BS)

1 McCutcheon RA, Pillinger T, Varvari I, et al. INTEGRATE: international guidelines for the algorithmic treatment of schizophrenia. *Lancet Psychiatry* 2025; **12:** 384–94.
2 Firth J, Siddiqi N, Koyanagi A, et al. The *Lancet Psychiatry* Commission: a blueprint for protecting physical health in people with mental illness. *Lancet Psychiatry* 2019; **6:** 675–712.
3 Green CA, Yarborough BJH, Leo MC, et al. The STRIDE weight loss and lifestyle intervention for individuals taking antipsychotic medications: a randomized trial. *Am J Psychiatry* 2015; **172:** 71–81.
4 Korman N, Stanton R, Vecchio A, et al. The effect of exercise on global, social, daily living and occupational functioning in people living with schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2023; **256:** 98–111.
5 Firth J, Solmi M, Wootton RE, et al. A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. *World Psychiatry* 2020; **19:** 360–80.

The International Guidelines for the Algorithmic Treatment of Schizophrenia (INTEGRATE) are a recently developed, internationally endorsed, consensus-based framework that provides an algorithmic approach to the pharmacological management of schizophrenia.[1] Unlike previous country-specific or region-specific guidelines that often lack structured decision-making frameworks,

INTEGRATE offers a standardised yet adaptable model, combining recent evidence, expert consensus (with representation from low-income and middle-income countries), and patient-centred perspectives.

However, the INTEGRATE framework does not sufficiently address the role of conventional antipsychotics (also referred to as first-generation antipsychotics), which continue to hold clinical relevance and utility in the evidence-based management of schizophrenia. The changing emphasis on the use of conventional to second-generation antipsychotics is not necessarily due to clear superiority in efficacy.[2] Many first-generation antipsychotics and second-generation antipsychotics have overlapping receptor profiles and clinical effects; however, these simplified terms are widely accepted. Treatment guidelines, which rely more on recent evidence than on the real-world effectiveness of antipsychotics, can inadvertently reinforce prescribing biases that favour second-generation antipsychotics, leading to a cycle wherein less studied—but still useful—medications in the first-generation antipsychotics category see reduced clinical use and decreasing research attention.[2,3]

When evaluating treatment choices, both efficacy and adverse effect profiles should be considered. Some first-generation antipsychotics have distinct advantages: for example, loxapine's inhaled formulation provides an alternative route of administration in acute agitation; trifluoperazine offers a unique advantage in treating severe comorbid anxiety with schizophrenia; and depot antipsychotics, such as haloperidol, flupentixol, and fluphenazine, are useful as clozapine augmentation strategies in clozapine-resistant schizophrenia.[4] However, these drugs receive no mention in newer treatment guidelines for schizophrenia, including INTEGRATE. Although first-generation antipsychotics are often associated with heightened risks of extrapyramidal symptoms, second-generation antipsychotics are more likely to contribute to metabolic complications, which are a major factor in the reduced life expectancy of individuals with schizophrenia. The INTEGRATE guidelines partly address this concern by explicitly favouring second-generation antipsychotics with lower adverse effect profiles. However, treatment decision making should empower patients to choose from the entire range of antipsychotics based on individual risk-to-benefit considerations, rather than being constrained by guideline-driven preferences for one class over another.

Another concern that warrants discussion in guideline development is the cost effectiveness of antipsychotics across diverse health-care systems. Although pricing differences between first-generation and second-generation antipsychotics might not be substantial in the UK, this is not the case worldwide.[5] Treatment accessibility varies significantly across regions, and a more detailed economic analysis of medication costs in different countries is essential to strengthen future iterations of the guidelines.

In summary, INTEGRATE offers an evidence-based, individualised approach to schizophrenia care, but optimising outcomes requires that its recommendations remain flexible, include first-generation antipsychotics, and reflect real-world clinical practice.

I declare no competing interests.

Satish Suhas
drsuhas@nimhans.ac.in

Department of Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore 560029, India

1 McCutcheon RA, Pillinger T, Varvari I, et al, and the INTEGRATE Advisory Group. INTEGRATE: international guidelines for the algorithmic treatment of schizophrenia. *Lancet Psychiatry* 2025; **12:** 384–94.
2 Dibben CRM, Khandaker GM, Underwood BR, et al. First-generation antipsychotics: not gone but forgotten. *BJPsych Bull* 2016; **40:** 93–96.
3 Leucht S, Huhn M, Davis JM. Should "typical", first-generation antipsychotics no longer be generally used in the treatment of schizophrenia? *Eur Arch Psychiatry Clin Neurosci* 2021; **271:** 1411–13.
4 Wagner E, Löhrs L, Siskind D, Honer WG, Falkai P, Hasan A. Clozapine augmentation strategies—a systematic meta-review of available evidence. Treatment options for clozapine resistance. *J Psychopharmacol* 2019; **33:** 423–35.
5 Avasthi A, Aggarwal M, Grover S, Khan MKR. Research on antipsychotics in India. *Indian J Psychiatry* 2010; **52** (suppl 1)**:** S317–40.

Authors' reply

We thank Nicholas Fabiano and colleagues, and Satish Suhas for their engagement with the International Guidelines for the Algorithmic Treatment of Schizophrenia (INTEGRATE)[1] and for their thoughtful comments.

Suhas suggests an increased focus on so-called first-generation antipsychotics is needed. Unlike other guidelines that use the first-generation and second-generation dichotomy, we deliberately avoided categories that do not align with clinical or pharmacological profiles.[2,3] Clinical effects overlap greatly between these groups: many older antipsychotics are associated with metabolic side-effects, and newer compounds can still produce extrapyramidal symptoms.[4,5] Moreover, no consistent pharmacological differences exist between these first-generation and second-generation antipsychotics.[2,3] This longstanding dichotomy is not useful in clinical practice or research.

INTEGRATE instead recommends personalising treatment based on side-effect profiles, and considering receptor binding profiles when switching antipsychotics. This approach facilitates the appropriate use of older medications such as chlorpromazine and haloperidol when clinically indicated. As Suhas highlights, INTEGRATE explicitly endorses shared decision making, enabling patients to choose from the full range of antipsychotics available. We also agree