

The evolution of long-acting antipsychotic treatments

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Long-acting antipsychotic treatments (LATs) have been shown to improve treatment continuity and prevent relapse in the management of schizophrenia and psychotic disorders. Furthermore, they appear to be associated with significant and sustained long-term effects while both levels of adherence and treatment frequency may play a role in minimizing treatment interruptions. With this Special Collection on LATs, we aimed to provide an extended scope and a balanced overview of recent developments and novel findings, as well as to address existing gaps and current controversies in the use of LATs, such as their early or trans-diagnostic application, the introduction of new and ultra-long-acting formulations, patient experience, and sex-specific considerations, as well as if, when and how to discontinue use. Furthermore, the Special Edition was seeking to cover functional and long-term patient-related outcomes and discuss whether emerging evidence should inform relevant guideline updates.

Not surprisingly, a number of contributions centered on the earlier use of LATs and their potential benefits. In their systematic review and meta-analysis,¹ Vita et al. found no significant differences emerging between LATs and oral antipsychotics (OAPs) for relapse/hospitalization prevention and acceptability across 11 head-to-head RCTs. However, LATs outperformed OAPs in nine subgroup analyses (in studies with patients with schizophrenia only, with indicators of higher quality and/or pragmatic design regarding relapse/hospitalization prevention (four subgroup analyses) and/or reduced all-cause discontinuation (five subgroup analyses)), without any instance of OAPs superiority versus LATs.

The topic of if, when, and how to discontinue antipsychotic medication has gained significant attention over recent years. In their papers,² O'Neil et al. argue that the abrupt cessation of LATs is not consistent with gradual hyperbolic tapering, despite their longer half-lives compared with oral formulations and may produce a rate of reduction in D2 blockade too great for many patients and may lead to withdrawal symptoms and/or relapse. Hence, they propose a model as to how best to reduce and discontinue commonly used decanoate-based LATs such as flupentixol, zuclopenthixol, and haloperidol as well as monthly aripiprazole injections and provide guidance regarding their dosing, frequency, and switch to oral equivalents.

Rightfully, there is also a heightened awareness pertaining to sex-specific treatment considerations more recently, and in their topical review Brissos and Balanza-Martinez shift their focus to the use of LATs in women.³ They highlight their significant underutilization in this patient population and address a number of biological factors and social aspects, such as pregnancy, lactation, contraception, and menopause, that are specific to women as well as their implications for the clinical management of women with SZ.

The trans-diagnostic application of antipsychotic medication including their long-acting formulations has been steadily increasing over the last decade and in their systematic review Bartoli et al.⁴ evaluate the real-world effectiveness of LATs in the management of Bipolar Affective Disorder. They found that across six mirror-image studies that compared relevant clinical outcomes, LATs treatment was associated with a significant

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reduction in number and length of hospitalizations as well as in the number of emergency department visits and hypo-/manic relapses in the year after LATs initiation, while the effect of LATs on depressive episodes was less clear.

Novel and ultra-long treatments, that is, LATs with longer dosing intervals appear to be associated with improved clinical outcomes and added real-world benefits in the management of schizophrenia and psychotic disorders. In fact, Paliperidone Palmitate six-monthly (PP6M) provides the longest dosing interval, twice-yearly dosing, among all currently available LATs. Garcia-Carmona et al.⁵ report results from the first real-world (4-year mirror-image and multi-centre) European study of patients initiating PP6M. Of particular note, patients demonstrate particularly high treatment persistence with 94% continuing treatment at 1 year.

In his intriguing contribution to the Collection, Emsley provides a critical review of the literature investigating longitudinal changes in brain structure (cortex, basal ganglia, and white matter) in individuals with schizophrenia including the effects of medication non-adherence and relapse.⁶ To quote the author “medication adherence may be an important factor that could explain the findings that brain volume reductions are associated with poor treatment response, higher intensity of antipsychotic treatment exposure and more time spent in relapse. Improved adherence via long-acting injectable antipsychotics and adherence-focused psychosocial interventions could maximize the protective effects of antipsychotics against illness progression. Volume reductions, therefore, do not necessarily imply tissue loss and volume increases are not necessarily beneficial.” So, while neither “less is more” nor “the more the merrier” necessarily apply here, treatment continuation and avoidance of treatment interruptions may (partly) explain or lead to positive changes.

Finally, in their Editorial,⁷ Kane and Rubio discuss some of the common misconceptions and barriers to LAT use in routine clinical practice by both clinicians and patients as well as why it is important to override them and how. They conclude that in their view “given the evidence of benefits and risks coupled with the consequences of psychotic relapse, we should less frequently be

asking ‘why?’ we should use a LAT and more frequently be asking ‘why not?’”

The findings of the studies included in this Special Collection have significant implications for future research and the development of novel treatments for psychotic and other neuropsychiatric disorders. Furthermore, the latest developments in the field may enhance patient experience and facilitate the collaborative process; thus help overcome common barriers to use in clinical practice and broaden the scope of application of long-acting treatments. Both current evidence and experience should be appropriately reflected in relevant, up-to-date guidelines.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Sofia Pappa: Conceptualization; Project administration; Resources; Visualization; Writing – original draft; Writing – review & editing.

Robin Emsley: Conceptualization; Writing – original draft; Writing – review & editing.

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Competing interests

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