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Guest Editorial

Pharmacological augmentation for people with treatment-resistant depression

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Summary

Long-term pharmacological augmentation is central to care for treatment-resistant depression, yet until recently no adequately powered trials have examined it. With three such studies now published, we highlight the hope they offer for improving outcomes in this underserved population while highlighting caution in interpreting their collective findings without careful consideration of methodology and clinical context. We consider these issues and their implications for guiding more personalised treatment decisions aimed at sustained benefit in routine practice.

Keywords

Augmentation; treatment-resistant depression; lithium; quetiapine; ketamine.

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Treatment-resistant depression (TRD) is a clinical challenge. Guidelines recommend two principal pharmacological strategies when initial antidepressants fail: switching to another antidepressant or augmenting the regimen with an additional agent.[1] Although TRD is usually defined as non-response to two adequate antidepressant monotherapies,[1] augmentation may offer some advantages over switching, even after a single antidepressant trial.[2] Although antidepressant–antidepressant combination strategies (e.g. adding mirtazapine to a selective serotonin uptake inhibitor) are commonly used in practice, guidelines generally prioritise pharmacological augmentation with lithium, quetiapine, aripiprazole and, increasingly, (es)ketamine (esketamine is the UK-licensed intranasal formulation but racemic ketamine is widely used intravenously (or via other routes) and is now also licensed in some other countries).[3]

Even following remission, residual depression, fluctuating symptoms and frequent relapse are common, usually necessitating long-term treatment in this illness.[1] Conversely, treatment guidelines to date have had to rely primarily on short-term trials (usually 6–12 weeks) due to an absence of adequately powered long-term data.

Three such long-term trials have now been published (Table 1); these show sustained benefits from augmentation with esketamine, quetiapine and pramipexole.

The Lithium versus Quetiapine in Depression (LQD) study[4] was a UK-based pragmatic randomised control trial (RCT) in which quetiapine demonstrated superiority over lithium augmentation for most, although not all, outcomes. The PAX-D study,[5] also UK-based, showed a clear benefit of pramipexole over placebo. ESCAPE-TRD,[6] an international RCT, reported benefits of esketamine nasal spray over quetiapine augmentation, including favourable cost-effectiveness despite substantially higher drug costs.

These studies were not without limitations. Patients and treating clinicians were unblinded in both the LQD and ESCAPE-TRD studies, and functional unblinding may have been a concern in PAX-D due to the distinct side-effect profile and high attrition due to side-effects in the pramipexole group. Expectancy effects may have been magnified in ESCAPE-TRD, given esketamine's novelty, supervised administration and non-oral route. In addition, LQD and PAX-D had smaller sample sizes than ESCAPE-TRD, and participant eligibility criteria in PAX-D and ESCAPE-TRD may have limited generalisability to real-world TRD populations where treatment-specific risks are clinically salient. In ESCAPE-TRD, manufacturer funding and trial coordination may have also influenced estimates of comparative benefit.

These findings raise important practical questions: should (es)ketamine now be considered earlier in clinical decision frameworks for TRD, ahead of quetiapine and lithium? And where – if anywhere – should pramipexole be positioned?

Our perspective is that, although the findings from these trials prompt a reconsideration of how augmentation options are selected, they do not justify a simple universal hierarchy of treatments. Instead, they expand knowledge around the available options and support a shift away from 'what comes first for everyone' to 'what works for whom', judged on durability of benefit, tolerability, clinical presentation and feasibility of delivery.

(Es)ketamine's promise is tempered by challenges that preclude it from being a first-line augmentation agent in most circumstances. These include high costs of delivery and monitoring, misuse/dependence potential, safety/tolerability considerations and interpretive issues in the evidence base (including imperfect blinding and a potentially inflated placebo response; the influence of participant self-selection and treatment expectations on clinical response between groups; and concerns around the completeness of adverse event reporting).[7] Whereas these constraints limit early positioning, (es)ketamine may be appropriate for selected patients where rapid benefit is a priority and service infrastructure allows safe delivery and monitoring.

Quetiapine and lithium remain mainstays with recognised limitations. The adverse effects of lithium are well documented but can be minimised with careful clinical management; lithium may be particularly indicated where suicide risk is elevated (as reflected in guideline recommendations[1]). Quetiapine is often considered relatively well tolerated but, over extended periods, confers metabolic, sedative and cardiovascular risks and it may be most suited to patients with prominent anxiety or insomnia.

Pramipexole appears promising, especially where anhedonia predominates. Its adverse-effect burden warrants consideration, notably nausea and dopamine-related impulse control difficulties; these may be attenuated by optimal doses, or by modified-release preparations, although further evidence is needed. Additionally, head-to-head and pragmatic data are needed to establish its position in augmentation treatment steps.

Substantial practical considerations remain. Access to care is a major barrier, with delayed diagnosis, limited access to specialist

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Table 1 Long-term randomised controlled trials of augmentation in TRD

Trial	Intervention(s)	Funder	Duration	*n*	Key findings
LQD (2025)	Lithium versus quetiapine	UK NIHR	52 weeks	212	Quetiapine superior in symptom reduction and cost-effectiveness
ESCAPE-TRD (2023)	Esketamine versus quetiapine	J&J	32 weeks	676	Esketamine superior in remission and relapse prevention
PAX-D (2025)	Pramipexole versus placebo	UK NIHR	48 weeks	151	Large effect size; tolerability concerns

TRD, treatment-resistant depression; LQD, Lithium versus Quetiapine in Depression; UK NIHR, United Kingdom National Institute of Health and Care Research (government health research funder); J&J, Janssen-Cilag International, under the umbrella of Janssen Pharmaceutical Companies of Johnson & Johnson.

services and prolonged use of ineffective antidepressants common.[8,9] This presents logistical challenges for implementing specialist evidence-based augmentation treatments more widely.

Collectively, these are the first adequately powered randomised trials to test augmentation beyond 6 months in TRD and they indicate durable benefit, addressing a longstanding evidence gap. This new evidence should meaningfully influence future treatment guideline updates. In particular, guidelines should incorporate the durability of benefit, tolerability, treatment burden and service feasibility, rather than relying primarily on short trials and simplified hierarchies. Implementation realities (delayed diagnosis, limited specialist capacity, prolonged use of ineffective treatments) must be tackled in parallel, otherwise potential benefits will not reach patients. The bottom line: TRD is treatable with pharmacological augmentation as a key option alongside other modalities. We need to prioritise matching treatments to patients and ensure that evidence-based recommendations translate into real-world care.

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Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Author contributions

A.J.C. initially conceptualised the editorial content. R.S. coordinated the work and wrote the first draft of the manuscript. R.S., V.L.N., M.B., J.R., P.J.C., D.A.C., A.H.Y. and A.J.C. contributed to conceptualisation, manuscript drafting and final approval for publication.

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