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Snips from the Journals

What's new in the management of depressive disorder? Key updates for clinicians

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Abstract

Background

Depressive disorder remains a leading cause of disability worldwide and continues to present significant challenges in clinical practice despite the availability of effective treatments. Recent advances have expanded understanding of the disorder and introduced new concepts and therapeutic approaches that have important implications for patient care. This article reviews selected developments relevant to practising clinicians, including the emerging concept of difficult-to-treat depression, the role of rapid-acting antidepressants such as ketamine and esketamine, evolving evidence on antidepressant discontinuation and hyperbolic tapering, the growing application of artificial intelligence and digital biomarkers in depression care, and recent progress towards more personalised treatment approaches. Collectively, these developments reflect a shift from a predominantly symptom-focused and standardised model of care towards more comprehensive, patient-centred, and individualised management. While several of these innovations remain under active investigation and are not yet routinely implemented in all clinical settings, they are increasingly influencing contemporary clinical practice and future treatment strategies. An understanding of these emerging developments will help clinicians make informed treatment decisions, optimise long-term outcomes, and deliver more personalised care for patients with depressive disorder.

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Depressive disorder is one of the leading causes of disability worldwide and continues to pose a major public health challenge. According to the World Health Organization, more than 330 million people are affected globally. In Sri Lanka, a recent systematic review and meta-analysis estimated the pooled prevalence of depression to be 19.4%, highlighting the considerable burden of depressive disorder in the local population. Despite the availability of effective pharmacological and psychological treatments, a substantial proportion of patients experience persistent symptoms, recurrent episodes, or incomplete functional recovery (1,2).

In recent years, several important developments have influenced the management of depressive disorder. New concepts such as difficult-to-treat depression, rapid-acting antidepressants, evolving approaches to antidepressant discontinuation, artificial intelligence in depression care, and precision psychiatry are gradually finding their place in clinical practice. This article highlights selected recent updates that are relevant to practising clinicians and discusses their implications for the contemporary management of depressive disorder.

Difficult-to-treat depression: Moving beyond treatment resistance

For many years, treatment-resistant depression (TRD) has been used to describe patients who fail to respond adequately to at least two antidepressants prescribed at an adequate dose and duration. Although this definition has been useful in both clinical practice and research, it focuses primarily on pharmacological treatment failure and does not adequately capture the complexity of many patients encountered in everyday clinical practice (3).

More recently, the concept of difficult-to-treat depression (DTD) has emerged as a broader and more patient-centred framework. The international consensus statement defines DTD as depression that continues to cause a significant burden despite usual treatment efforts, in which further therapeutic interventions remain clinically worthwhile. Unlike TRD, DTD is not determined by the number of unsuccessful antidepressant trials but by recognising that persistent illness often reflects the complex interaction of patient-related, illness-related and treatment-related factors. Diagnostic uncertainty,

psychiatric and physical comorbidities, substance misuse, poor treatment adherence, adverse effects and psychosocial adversity may all contribute to the persistence of depressive symptoms and ongoing illness burden (3,4).

The management of DTD therefore begins with a comprehensive reassessment rather than repeated sequential antidepressant trials. Re-evaluation of the diagnosis, optimisation of pharmacological treatment, augmentation strategies, evidence-based psychological therapies, management of comorbid conditions, and attention to functional recovery are all integral components of care. Accordingly, the management of DTD shifts the focus from achieving symptom remission alone towards reducing illness burden, improving psychosocial functioning and quality of life, and providing personalised multidisciplinary care based on individual patient needs (3,4).

Rapid-acting antidepressants: The role of ketamine and esketamine

Although conventional antidepressants remain the cornerstone of pharmacological treatment for depressive disorder, their therapeutic effects are not immediate, and many patients require several weeks to achieve full clinical benefit. Electroconvulsive therapy (ECT) remains an effective treatment option when a rapid antidepressant response is clinically indicated; however, there has long been a need for a rapidly acting pharmacological treatment. The introduction of ketamine and its S-enantiomer, esketamine, has begun to address this important therapeutic gap and represents one of the most significant advances in the pharmacological management of depressive disorder in recent years (5).

Unlike conventional monoaminergic antidepressants, ketamine and esketamine exert their antidepressant effects primarily through modulation of the glutamatergic system via N-methyl-D-aspartate (NMDA) receptor antagonism. This novel mechanism has broadened our understanding of the neurobiology of depression and introduced an alternative therapeutic approach for patients who do not respond adequately to conventional antidepressants. Randomised controlled trials and subsequent meta-analyses have demonstrated a rapid reduction in depressive symptoms, often within 24 hours of administration, with benefits sustained over the following days. Ketamine has also demonstrated rapid reductions in suicidal ideation in some studies; however, evidence regarding its sustained anti-suicidal effects remains less consistent. Intranasal esketamine has been approved in several countries, in combination with an oral antidepressant, for adults with treatment-resistant depression (5,6).

Despite their promising efficacy, ketamine and esketamine should be regarded as specialised treatment options rather than routine first-line antidepressants. Current clinical guidelines recommend their use in carefully selected patients, particularly those with treatment-resistant depression, following a comprehensive clinical assessment. Administration should occur in appropriately equipped healthcare settings with monitoring for transient adverse effects, including dissociation, sedation, and increases in blood pressure. The relatively high cost, limited availability, uncertainty regarding long-term maintenance treatment, and potential for misuse remain important considerations when selecting suitable patients. Consequently, ketamine and esketamine should be integrated into a comprehensive treatment plan that includes ongoing pharmacological management, psychological interventions, and long-term follow-up (5,6).

Antidepressant discontinuation: New evidence and practical considerations

The approach to antidepressant discontinuation has undergone considerable revision in recent years. Earlier guidance generally regarded withdrawal symptoms as short-lived and self-limiting, and recommended relatively short tapering schedules. However, accumulating evidence has challenged this view, indicating that discontinuation symptoms affect a clinically relevant proportion of patients and, in some, may be severe, prolonged, and clinically significant. These findings have prompted important revisions to clinical guidelines and emphasised that antidepressant discontinuation should be considered an integral component of depression management rather than simply the final stage of treatment (7,9).

An important consequence of this evolving evidence is the need for greater diagnostic vigilance during antidepressant discontinuation. Although the distinction between withdrawal symptoms and relapse has long been recognised, greater appreciation of the persistence and clinical significance of withdrawal symptoms has reinforced the importance of careful assessment during antidepressant tapering. Evaluating the temporal relationship to dose reduction, the timing of symptom onset, and the presence of characteristic withdrawal features can help distinguish withdrawal symptoms from depressive relapse. Failure to recognise discontinuation symptoms may result in unnecessary dose escalation or inappropriate continuation of antidepressant treatment (8,9).

Traditional tapering schedules for serotonergic antidepressants often recommend reducing doses by fixed amounts over a relatively short period. More recent

pharmacological evidence suggests that this linear approach does not reflect the relationship between antidepressant dose and serotonin transporter occupancy. Consequently, hyperbolic tapering has emerged as a pharmacologically informed strategy, particularly for serotonergic antidepressants such as SSRIs and SNRIs. Unlike linear tapering, which reduces the dose by equal amounts at each step, hyperbolic tapering involves progressively smaller dose reductions as treatment approaches cessation. This approach is based on the observation that the relationship between antidepressant dose and serotonin transporter occupancy is non-linear; consequently, equal dose reductions produce progressively larger pharmacodynamic effects at lower doses, increasing the likelihood of withdrawal symptoms. The aim of hyperbolic tapering is therefore to produce more gradual pharmacodynamic changes throughout the tapering process, thereby minimising the risk of withdrawal symptoms. Nevertheless, tapering schedules should be individualised according to the antidepressant prescribed, duration of treatment, previous discontinuation experiences, patient preference, and the emergence of withdrawal symptoms during dose reduction (7).

These developments reinforce the importance of considering antidepressant discontinuation as part of ongoing treatment planning rather than addressing it only at the point of treatment cessation. Shared decision-making, patient education, regular clinical follow-up, and personalised tapering schedules should form part of routine antidepressant management. A thoughtful and patient-centred approach to discontinuation should now be regarded as an essential component of high-quality depression care (7,9).

Artificial intelligence in depression care

The management of depressive disorder is becoming increasingly data-driven. Advances in artificial intelligence (AI) are enabling the integration of clinical information with longitudinal symptom assessments, patient-reported outcomes, and emerging digital biomarkers, with the potential to support earlier detection of symptom change, prediction of treatment response, and more personalised follow-up. Digital biomarkers refer to objective behavioural and physiological data derived from smartphones, wearable devices, speech characteristics, sleep patterns, and physical activity. These technologies have the potential to continuously monitor patients beyond traditional clinic visits, facilitating earlier identification of relapse and more timely clinical intervention. By integrating longitudinal symptom measures with digital biomarkers, AI has the potential to support more responsive and individualised treatment decisions throughout the course of illness, representing an important step towards more precise and personalised depression care (10-13).

Although these developments are promising, AI should currently be regarded as an adjunct to, rather than a replacement for, comprehensive clinical assessment and decision making in depressive disorder. Most AI-based tools require further prospective validation before widespread implementation in routine clinical practice, and their recommendations should always be interpreted within the broader clinical context. The successful integration of AI into depression care will depend on rigorous clinical validation, responsible implementation, and ensuring that clinical judgment and the therapeutic relationship remain central to the management of depressive disorder (10-13).

Personalising the treatment of depressive disorder

One of the greatest challenges in the management of depressive disorder is the inability to accurately predict which treatment is most likely to benefit an individual patient. Although treatment selection is guided by careful clinical assessment, symptom profile, previous treatment response, comorbidities, adverse effect profiles, and patient preferences, patients with apparently similar clinical presentations often exhibit markedly different responses to the same antidepressant. This variability has stimulated increasing interest in identifying objective predictors of treatment response that may support more individualised treatment decisions (10,14,15).

Recent advances have focused on combining multiple sources of information rather than relying on a single biomarker. Genetic and pharmacogenomic factors, inflammatory biomarkers, neuroimaging findings, cognitive characteristics, and digital biomarkers are increasingly being investigated for their potential to predict antidepressant response and longer-term clinical outcomes. Rather than replacing clinical judgement, these approaches aim to complement conventional clinical assessment by improving treatment selection, reducing unnecessary changes in antidepressant treatment, and shortening the time taken to achieve remission (10,15)

Some components of personalised depression care, particularly pharmacogenomic-guided antidepressant prescribing, have already been incorporated into clinical practice in selected settings. However, no single biomarker currently provides sufficient accuracy to guide treatment decisions independently. The greatest potential lies in integrating careful clinical assessment with pharmacogenomic, biological, and digital information to support more precise and individualised treatment selection for patients with depressive disorder (10,14,15).

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