Column: New in Psychopharmacology

A SELECTIVE SUMMARY OF PSYCHOPHARMACOLOGY RESEARCH PUBLISHED IN FIRST HALF OF 2017

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There is a fear that the golden age of psychopharmacology discoveries is behind us and that we have reached a dead end.[1] In the past, serendipity and the observation of a large number of patients in close proximity contributed enormously to the discovery of new medications. However, current circumstances do not facilitate such breakthroughs. Efforts to design molecules with predictable effects have, so far, failed to yield promised rewards. We continue to polish, reclassify, and repurpose in order to create 'me too' medications. A few new treatments have emerged in 2017 and three of them are covered in this summary.

NEW RAPID ACTING MEDICATION FOR POSTPARTUM DEPRESSION

Depression in the postpartum stage is seen in 10-20% of all mothers. It is a leading cause of maternal mortality and can have long-standing negative consequences on the child. Changes in plasma allopregnanolone, especially the abrupt decrease postpartum, is linked to the precipitation of depression.[2] Plasma allopregnanolone is a neuroactive steroid with potent positive modulatory effect on extra-synaptic GABA receptors. Rapid metabolism and poor bioavailability prevent the use of oral form of allopregnanolone. Brexanolone, an intravenous formulation of allopregnanolone, is showing promise in the treatment of postpartum depression.[3]

Kanes et al. carried out a randomised double blind, parallel group placebo controlled study across four sites in USA.[3] Twenty-one women with severe depression, within the initial six months of postpartum period, participated. A single continuous IV infusion of brexanolone was administered for 60 hours. Outcome assessments were done on day 30. At the end of 60 hours, the HAMD total score decreased by 21 points in the brexanolone group compared with 8.8 points in the placebo group ($p = .0075$, effect size=1.2). This was more or less maintained up to day 30 (the study end point). At 60 hours, seven out of ten patients receiving brexanolone met remission criteria compared with one in the placebo arm. On day 30, seven patients reached remission on active treatment compared to two with placebo. The medication was well tolerated. Overall side effects were higher in the placebo arm. Tachycardia, sedation, and dizziness were reported with brexanolone.

This study provides the first robust evidence of the effectiveness of brexanolone, an extra-synaptic GABA-A receptor modulator, in treating postpartum depression. The rapid onset of action is particularly useful given the serious impact (e.g., disrupted bonding) of the illness on mother and baby. This is a promising start and if replicated is likely to find its way into clinical practice, given the key role played by postpartum depression in maternal mortality.

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POSTOPERATIVE DELIRIUM CAN BE PREVENTED

Postoperative delirium occurs in up to 50% of patients, with elderly being more susceptible. Delirium is associated with higher morbidity and mortality.[1] There are no medications to reliably prevent such delirium.

Dexmedetomidine, a highly selective alpha 2 adrenoreceptor agonist, is increasingly used as a sedative in intensive care units (ICU). In ventilated patients, use of dexmedetomidine has been shown to result in less delirium when compared to benzodiazepines. It has sedative, anxiolytic, and analgesic properties. It also causes minimal respiratory depression.

Su et al. conducted a randomised double blind, parallel-arm placebo controlled trial among older adults (65 years or more) admitted to ICU following elective cardiac surgery and with no previous known mental illness.[2] Consecutively recruited patients were randomly allocated to the two experimental arms. Medication was administered as continuous IV at a rate of 0.1 microgm/kg per hour within one hour after ICU admission until 0800 h on the day following the surgery. Standard delirium preventing strategies like repeated reorientation, cognitive stimulation, early mobilisation, and sleep promotion were applied to all patients. Patients who developed delirium were treated with haloperidol. Confusion Assessment Method for the ICU (CAM-ICU) was used to assess delirium.

Seven hundred patients were enrolled. During the seven day follow up, 23% of patients on placebo developed delirium compared with 9% on dexmedetomidine (OR 0.35, P<0.0001). Intubation status did not have any effect on the outcome. All three types of delirium (hypoactive, hyperactive, and mixed) were decreased by the medication. The delirium prevention effect was significant when the duration of infusion was 12.5 hours or longer. The medication also reduced non-delirium complications. Median time to intubation was shorter in the treatment group. Bradycardia and hypotension did not differ between groups.

This study establishes the prophylactic effect of dexmedetomidine infusion on delirium, in elderly patients admitted to the ICU, during the seven days following surgery. The beneficial effect could be due to a reduction in hypoxemia, improvement in sleep, modulation of inflammation, haemodynamic stabilisation, and neuroprotective effects. The effects reported during this study could be due to the reduction in use of sedative medications, which are known to cause delirium. Further work is required to confirm if the effects are generalizable to non-ICU patients and non-surgery patients in ICU.

This novel application of dexmedetomidine is likely to attract more attention in the coming years. At the moment, it can only be given in highly monitored intensive care units due to the cardiac effects associated with higher doses.

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VALBENAZINE FOR TARDIVE DYSKINESIA

Tardive dyskinesia (TD) is a disabling condition that develops in 20-30% of patients who have been chronically exposed to dopamine receptor blockers.[1] Previously, there were no approved medications to treat this condition. Vesicular monoamine transport inhibitors (VMAT2) are a class of medications that can reduce the movement side effects of dopamine

blockade. The VMAT2 inhibitor, tetrabenazine is beneficial in treating chorea and has shown some temporary benefit in TD also. Valbenazine is a new highly selective VMAT2 inhibitor. Hauser et al. conducted a trial for six weeks using a double blind placebo controlled randomised controlled design.[2] All participants in the trial had suffered from TD for at least three months; their mental and physical health was rated as stable. Valbenazine was given as a single daily dose of either 40mg or 80mg. The outcome measure was Abnormal Involuntary Movement Scale (AIMS) dyskinesia score at week 6. Two hundred and thirty-four patients were recruited; two thirds of participants had schizophrenia and 76.8% were taking atypical antipsychotics. In the 80mg group, at week 6, the AIMS dyskinesia score was -3.2 compared with -.1 for placebo ($p<0.001$; effect size=0.90). Valbenazine lower dose group also showed significant reduction compared with placebo. (-1.9 vs -0.1; $p=0.002$; effect size=0.52). Medication group reported more sedation, akathisia and dry mouth. Overall, the medication was well tolerated. However, a participant allocated to the active arm died suddenly; this could be due to a cardiovascular event. The study did not reveal any ECG changes associated with the medication. The Number Needed to Treat (NNT) for 80 mg/day dose is calculated as 4 based on 40% response with medication Vs 8.75% in placebo. FDA has now approved this medication for the treatment of TD. The recommended starting dose is 40 mg/day; this can be increased to 80 mg/day after one week. Valbenazine may prolong QTc interval and therefore, the product literature advises to avoid concomitant use of QTc prolonging medications.

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