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Letter to the Editor

RAADs (Rapidly Acting Anti-depressants)—A quantum leap?

Although there seems a fixed time course to remission inherent to MDD, data accrues speaking to the idea of possible rapid onset sustained antidepressant response. It holds true that different modalities of pharmacotherapy can have different time courses to effect antidepressant response.

Decades of experience with standard monoaminergic antidepressants have showed that a meaningful clinical response could take 4–6 weeks for most patients. Different strategies have since emerged not only to enhance the efficacy but also to hasten the time to antidepressant response. Indeed, early and optimal treatment is an important determining factor in the overall prognostication in MDD, including time to antidepressant response, remission, and likelihood of recurrence (Naguy et al., 2018).

Parenteral Route and Pulse-loading have been attempted on the premise that intravenous administration may achieve more rapid plasma steady state and improved bioavailability bypassing first-pass metabolism. Buoli et al. (2017) found daily iv clomipramine or trazodone produced statistically significant improvements within the one week of iv administration.

Add-on Strategies have been trialled, including pindolol, a β-blocker with $5HT_{1A}$ antagonistic activity, and stimulants. A meta-analysis has attested to the efficacy of add-on pindolol consistently demonstrating early benefit over placebo at 2 weeks of treatment (Ballesteros and Callado, 2004). An open-label study has also demonstrated that methylphenidate could enhance the time to response to TCA (Gwirtsman and Guze, 1989).

ECT can generally effect a more rapid response than the classical monoaminergic antidepressants. Folkerts et al. (1997) demonstrated patients in ECT group had a 15-point drop in HAM-D vs. 3-point improvement in paroxetine group by end of one week of treatment ($P < .001$)

Sleep Deprivation in a meta-analysis had a rapid onset of antidepressant effect in approximately half of subjects treated showing improvement within 48 h of a single night of deprivation (Hemmeter et al., 2010). This might be related to rectifying circadian misalignment, clock genes, plasticity-associated genes …

Broad High-trapping Glutamatergic Modulators including ketamine, esketamine and 2R, 6R-hydroxynorketamine. In a double-bind, placebo-controlled cross-over study for MDD and BD subjects, ketamine infusion (0.5 mg/kg for 40 min) induced antidepressant effects within 2 h. Within 24 h, 70% of study population had responded to ketamine, and 35% retained the antidepressant effect of ketamine at 1 week post-infusion (Zarate et al., 2006). The newly FDA-approved esketamine (Spravato) nasal spray, the *S*-enantiomer of ketamine, has been similarly found quite effective for TRD (Daly et al., 2018). Mechanisms are related to NMDAR antagonism, AMPA activation, GABAergic modulation, glutamate surge, opioid system involvement, increased BDNF expression …

Subunit-Specific NMDA Receptor Antagonists including rapastinel, NMDAR glycine site partial agonist, is being investigated as a potential antidepressant. It has been demonstrated that doses of 5- or 10- mg/kg induce reduction of depression symptomatology within days safely (Preskorn et al., 2015).

GABAergic Agents including the recently FDA-approved brexanolone (Zulresso) has been demonstrated to have a rapid onset of sustained antidepressants effects in women suffering from postpartum depression (Meltzer-Brody et al., 2018).

Psilocybin as a $5HT_{2A}$ agonist has been previously used in facilitated psychotherapy. A number of trials have shown psilocybin to rapidly and durably improved symptoms of depression and anxiety in patients with life-threatening cancer diagnoses (Ross et al., 2016).

It seems that RAADs, beyond specific neurotransmitter level, induce neuroplastic changes that can account for antidepressant superiority and sustainability.

It is also crucial not to ignore other non-specific factors that may influence the rate of onset for antidepressant responses, e.g. expectations, treatment unblinding, unique personal experiences, differences in study design …

To reckon, the long sought-after RAADs finally appear within reach. Treatment modalities providing clinically meaningful responses in the scale of hours/days are now readily available. Time would tell about their real placement in the algorithms of psychopharmacotherapy of MDD.

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