



Letter to the Editor

What's around the corner in the niche of psychopharmacotherapy of major depressive disorder?



Sorely, current first-line antidepressants, though rampant, effect remission in only one-third of patients whilst another third remain treatment-resistant after multiple trials, as shown in the landmark STAR*D study (Naguy et al., 2018). This implies that the monoaminergic hypothesis of depression is over-simplistic and cannot by any means fully explain this clinical outcome. This mandates exploring new venues that can dissect the sophisticated neurobiology of MDD and meanwhile providing a scaffold for novel therapeutic targets. This recently elucidated, yet not fully comprehended, complex nature of MDD reflects the heterogeneity of clinical phenotypes (Dan and Keshavan, 2017).

1. Inflammatory pathway

Potential targets include:

- Inflammatory cytokine antagonists- e.g. TNF- α antagonist; infliximab (Patra, 2018). This might be appropriate for patients with high baseline inflammatory biomarkers (serum hs-CRP ≥ 2 mg/L)
- NSAIDs- e.g. COX-2 inhibitor; celecoxib (400 mg/d) in an RCT of 37 MDD subjects, adjunctive to fluoxetine, significantly reduced depression rating scores compared to placebo. (Akhondzadeh et al., 2009)
- Natural anti-inflammatory agents- e.g. omega-3 polyunsaturated fatty acids. Several trials and meta-analyses of omega-3 with $\geq 60\%$ EPA content, adjunctive to SSRIs suggest that omega-3 may exert significant antidepressant effects (Gertsik et al., 2012)
- Tetracycline antibiotics- e.g. doxycycline has shown a promising preclinical antidepressant effects (Ferreira Mello et al., 2013)

2. Oxidative/nitrosative stress pathway

Potential targets include:

- N-acetyl cysteine; precursor of the antioxidant glutathione. This is more relevant to bipolar depression. (Berk et al., 2008)

3. HPA (hypothalamic-pituitary-adrenal) axis pathway

Potential targets include:

- Cortisol synthesis inhibitors- e.g. metyrapone. An RCT of MDD patients has found that adjunctive metyrapone therapy is superior to placebo and exhibits faster onset of antidepressant action, as well as a sustained antidepressant effect (Jahn et al., 2004)
- Oxytocin- a powerful suppressor of HPA axis activity
- Endogenous neurosteroids- e.g. dehydroepiandrosterone (DHEA). A 6-week, RCT of 22 MDD patients found significant improvement in depression rating scale scores in patients randomized to take DHEA

compared to those receiving placebo (Schmidt et al., 2005)

4. Glucose metabolism pathway

Potential targets include:

- Incretinomimetics- Preclinical studies suggest that GLP-1 analogues improve cognition and reduce depressive-like behaviours in murine models. (McIntyre et al., 2013)
- Insulin sensitizers- e.g. pioglitazone. A recent RCT of adjunctive pioglitazone, found it improving depression rating scale scores and glucose metabolism in treatment-resistant MDD patients (Lin et al., 2015)

5. Bioenergetics pathway

Potential targets include:

- Mitochondrial modulators- e.g. creatine. Open-label trials of adult and adolescent treatment-resistant depression (TRD) patients given 3–5 g creatine adjunctively reported improved mood throughout the studies and at endpoints. (Rotiman et al., 2007)

6. One-carbon cycle pathway

Potential targets include: (Papakostas et al., 2012)

- SAME (S-Adenosyl-Methionine). Several studies suggest SAME adjunctively predictably and significantly enhances antidepressant effects
- L-Methyl-Folate. It has similarly repeatedly been shown to improve depression symptoms.

7. Neurotrophin signalling pathway

Potential targets include:

- Erythropoietin

8. Opioids pathway

Potential targets include:

- MOR modulators- e.g. buprenorphine has shown some promise as a possible therapeutic for TRD in a small open-label trial of 10 subjects. (Stanciu et al., 2017)

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9. Cholinergic system pathway

Potential targets include:

- Anti-muscarinic- e.g. scopolamine. Oral scopolamine as an adjunctive treatment for moderate to severe MDD has been shown to be a safe and efficacious treatment. (Khajavi et al., 2012)
- nAChRs antagonists- e.g. varenicline; it appears to exert both effects as an antidepressant as well as facilitate smoking cessations in smokers with TRD (Philip et al., 2009)

10. Glutamatergic system pathway

Potential targets include (Naguy, 2019a,b)

- Broad high-trapping glutamatergic modulators- e.g. ketamine (Gurnani and Khurshid, 2017) and esketamine. In a DBRCT cross-over study for MDD and BD subjects, ketamine infusion (0.5 mg/kg for 40 min) induced antidepressant effects within 2 h. Within 72 h, 70% of the study population had responded to ketamine, and 35% retained the antidepressant effect of ketamine at 1 week post-infusion.
- NMDAR antagonists- e.g. dextromethorphan
- Subunit-specific NMDAR antagonists- e.g. traxoprodil, D-cycloserin (DCS), rapastinel. DCS, in an RCT of 23 MDD patients, at higher doses exerted significant antidepressant effects as reported by both HAM-D and BDI scores. Rapastinel, NMDAR glycine site partial agonist, in a phase IIb study suggested that 5 or 10 mg/kg exerting a significant antidepressant response at 1-week post-administration.
- Glutamate modulators- e.g. riluzole; in a 19 patient, open-label study of 100–200 mg/d as monotherapy in TRD, significant improvement was noted in all patients beginning at week 3.

11. GABA (Gamma-aminobutyric acid) system pathway

Potential targets include:

- GABA_A positive allosteric modulator- e.g. brexanolone has been shown to have a rapid onset of sustained antidepressant effects in women suffering from postpartum depression (Naguy, 2019a,b)

12. Hallucinogens and serotonergic pathway

Potential targets include:

- Psilocybin- with 5HT_{2A} agonist properties. RCTs have demonstrated psilocybin to rapidly and durably improve symptoms of depression and anxiety in patients with life-threatening cancer diagnoses. (Patra, 2016)

For many targets discussed above, preclinical and early clinical evidences are promising, but the efficacy of targeting these pathways remains yet to be established in everyday practice awaiting replication in large-scale trials to define its real place in the psychopharmacotherapy algorithms of MDD.

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Authors declare no competing interests.

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