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Valproate for schizophrenia: ambrosia?

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Letter to the Editor

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Dear Sir,

In a recent Cochrane Systematic Review,[1] valproate had only a flimsy evidence-base in the pharmacotherapy of schizophrenia driven largely by open trials. It addressed chiefly aggressive and affective domains as "add-on" to ongoing antipsychotic treatment.[2] This might be through downstreaming of signal transduction. Moreover, it makes better sense when combined with clozapine especially to safeguard against the latter's epileptogenicity at higher doses, typically above 600 mg/d, by virtue of inhibiting repetitive firing and voltage-gated Na/K-channel blockade.[3] Valproate-clozapine pharmacokinetic interactions should be borne in mind where previous studies have showed no effect, mild inhibition, or induction of clozapine metabolism.[4] Moreover, dynamic interactions including myelosuppression, oversedation and confusion, and metabolic derangement have been reported in literature.[5]

Nonetheless, mechanistically, valproate is GABA potentiator. GABA deficiency is well established in the neurobiology of schizophrenia. So, correcting this deficit might enhance dopaminergic blockade in the mesolimbic pathway, and attenuate serotonergic input in mesocortical pathway.[6] Moreover, as an allosteric enhancer of $GABA_A$ inhibition, valproate might rectify a fundamental neurobiological underpinning in catatonic syndrome. Kruger and Braunig[7] have reported on a successful intravenous valproate treatment of severe catatonia. Furthermore, valproate possesses dopaminergic blockade activity, and ergo, the use in Sydenham's chorea[8] and the reported extrapyramidal syndromes.[9] More interestingly, valproate is histone deacetylase inhibitor. The increased acetylated histone content has been demonstrated to prevent methionine-induced releen promoter hypermethylation and normalize schizophrenia-like behaviors in mice.[10] All these pharmacodynamic actions (Table 1) would converge to translate clinically into putative antipsychotic properties of valproate.

Table 1. Mechanisms of Action of Valproate.

- VGS/KC blockade
- GABA potentiator
- Signal transduction downstreaming
- PK-C inhibition
- DA blockade
- 5HT modulation
- ↓GHB
- Histone deacetylase inhibition
- Anti-glutamate
- ↑ Bcl-2

Valproate, in addition, has been shown to be neuro-protective. It also induces the anti-apoptotic Bcl-2. It has anti-glutamate actions, and hence protects against glutamate excitotoxicity,[11] typically seen with neuro-progression in treatment-resistant schizophrenia.[12]

Quo Vadis? Valproate use in schizophrenia, despite the evidence, is multi-folded transcending anti-aggressivity and thymoleptic actions to bona fide antipsychotic actions and ultimately neuroprotective actions. It is rather an art than science!

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References

1. Wang Y, Xia J, Helfer B, Li C, Leucht S. Valproate for schizophrenia. *Cochrane Database Syst Rev*. 2016;**24**(11): CD 004028
2. Strassnig MT, Nascimento V, Deckler E, *et al.* Pharmacological treatment of violence in schizophrenia. *CNS Spectr*. 2019;1–9. doi: 10.1017/S1092852919001226.
3. Davis LL, Ryan W, Adinoff B, *et al.* Comprehensive review of the psychiatric uses of valproate. *J Clin Psychopharmacol*. 2000;**20**(suppl 1):1S–17S.
4. Diaz FJ, Eap CB, Ansermot N, *et al.* Can valproic acid be an inducer of clozapine metabolism? *Pharmacopsychiatry*. 2014;**47**(3):89–96.
5. Roerig JL. Clozapine augmentation strategies. *Ment Health Clin*. 2019;**9**(6):336–348.

6. Naguy A. Benzodiazepines in schizophrenia: Nemesis or Nirvana? *Indian J Psychol Med*. 2017;**39**:547–548.
7. Kruger S, Braunig P. Intravenous valproic acid in the treatment of severe catatonia. *J Neuropsychiatry Clin Neurosci*. 2001;**13**:303–304.
8. Cardoso F. Sydenham's chorea. *Curr Treat Options Neurol*. 2008;**10**: 230–235.
9. Sasso E, Delsoldato S, Negrotti A, Mancia D. Reversible valproate-induced extrapyramidal disorders. *Epilepsia*. 1994;**35**:391–393.
10. Tremolizzo L, Doueiri MS, Dong E, *et al.* Valproate corrects the schizophrenia-like epigenetic behavioural modifications induced by methionine in mice. *Biol Psychiatry*. 2005;**57**:500–509.
11. Vajda F. Valproate and neuroprotection. *J Clin Neurosci*. 2002;**9**:508–514.
12. Naguy A, Alamiri B. Ultra-treatment resistant schizophrenia—where do we stand? *Asian J Psychiatr*. 2019;**44**:95–96.

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