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Living in a Pharmacologically Imperfect World

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Dr Andrade's[1] and Dr Freeman's[2] thoughtful comments about the teratogenic and neurodevelopmental risks of valproate in pregnancy underscore a broader and more fundamental dilemma throughout all of medicine, involving the balance of risks and benefits. All else being equal, valproate is indisputably a nonpreferred treatment option for sexually active women of reproductive potential. In an ideal world, as Dr Freeman notes, prescribers should pretend it does not exist, and instead favor alternative psychotropics. However, in the nonideal real world, everything we could prescribe carries potential risks for serious adverse effects. In patients with bipolar disorder who are sexually active, one might favor a second generation antipsychotic over valproate and instead negotiate the risks for weight gain and metabolic dysregulation—including a possible 1.3-fold increased risk for gestational diabetes[3]—as well as a 2.6% annualized risk for tardive dyskinesia.[4] Alternatively, one could favor lithium, perhaps comforted by more tempered modern reappraisals of the real risk for cardiac valve malformations,[5] although debate in this area remains ongoing[6]; and, one must then also negotiate possible (albeit rare) obstetrical complications such as polyhydramnios and floppy baby syndrome. Importantly, how confidently can one presume that lithium will be efficacious for a given individual? Lithium has been shown to produce a robust prophylactic effect in less than 10% of bipolar disorder patients.[7] It appears inferior to valproate in multiepisode patients[8] and those with mixed features[9] or comorbid alcohol use disorders.[10] Furthermore, a recent meta-analysis observed that lithium exerts a relatively small effect for symptoms of bipolar depression (standardized mean difference = 0.24).[11]

Lamotrigine seems relatively safe in pregnancy, but it confers minimal protection against mania as compared to depression,[12] making its psychotropic profile vastly different from valproate or lithium. In the real world, one-third or more of bipolar disorder patients find themselves taking 3 or more psychotropic drugs,[13] driven often by depressive illness burden and incomplete symptom remission with simpler regimens; use of extensive polypharmacotherapy in itself is nonideal in pregnancy, as each added medication introduces additional unknown variables into the equation for a safe pregnancy outcome.

How does one then choose the *least imperfect* treatment option in the nonideal pharmacologic world of bipolar disorder in general, with superimposed pregnancy risk in particular? Likely, the only viable solution to the varied Hobson's choices inherent to psychopharmacology is to undertake risk-benefit analyses on a case-by-case basis, taking into consideration past treatment response, illness severity, relapse risk, and viable alternatives. Certainly, if and when a better and safer alternative to valproate exists, it warrants preferred status. However, the risk for relapse and functional impairment in bipolar disorder remains high even with state-of-the-art care,[14] making it a risky proposition to advise an absolute moratorium on any treatment that could help to avert its inordinately high morbidity and mortality.

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