Reply

Eva Feldman, MD, PhD, FAAN

We thank Drs Lang and Obeso for their perspectives on our article.[1] As described in our article and their letter, the mechanisms underlying neurodegenerative diseases are complex and therefore require multiple different treatment strategies. Because Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal muscular atrophy, and Parkinson's disease (PD) are therapeutically challenging disorders, there is increasing interest in cellular therapies. Current research is centered on the ability of stem and progenitor cells to provide direct replacement of diseased or lost cells, enhance neuronal circuitry, and enrich the local neuronal environment. Clearly, it is a combination of these factors that contributes to the attractiveness of stem cells as a potential therapy for complex neurodegenerative disorders, including PD.

We fully agree with Drs Lang and Obeso that PD is characterized by a complex loss of cell types and pathways. Yet while multiple cell types are affected in PD, classical approaches to cellular therapies over the past 2 decades have focused on replacement of lost dopaminergic neurons.[2–5] This has yielded promising results in vivo and modest functional improvements in patients. In a review article, we contend that we should provide the state of current research, and improving dopaminergic neuronal replacement remains the topic of numerous preclinical and clinical studies for PD.[2–5] Given the complexity of PD pathogenesis, however, we agree with Drs Lang and Obeso that current and future research should focus on the use of cellular approaches to support essential circuitry and all affected cell types in PD.[2,5] These multifaceted roles for emerging cellular therapies represent highly important and promising mechanisms of neuroprotection for PD. Most likely, combining cellular replacement with multidimensional support is essential for neuroprotection not only to dopaminergic neurons but to all other cell types and neuronal pathways affected by PD.

Overall, the capacity of stem cell technologies to treat neurodegenerative diseases is still a relatively new concept, and much work remains to be done before these approaches progress into realistic and tangible clinical treatments and cures. We acknowledge that there are remaining issues to address and that it can take over a decade to translate promising treatments to the clinic.[1,3] With continued advances in stem cell technologies and continued comprehension of mechanisms responsible for disease onset and progression, however, we can learn from previous results and evolve new innovative approaches for treating neurodegenerative disorders to maximize the potential of stem cell therapies and support the growing public hope.

Potential Conflicts of Interest

Nothing to report.

Department of Neurology, University of Michigan, Ann Arbor, MI

References

1. Lunn JS, Sakowski SA, Hur J, et al. Stem cell technology for neurodegenerative diseases. Ann Neurol 2011;70:353–361.
2. Ma Y, Peng S, Dhawan V, Eidelberg D. Dopamine cell transplantation in Parkinson's disease: challenge and perspective. Br Med Bull (in press).
3. Brundin P, Barker RA, Parmar M. Neural grafting in Parkinson's disease: problems and possibilities. Prog Brain Res 2010;184: 265–294.
4. Arenas E. Towards stem cell replacement therapies for Parkinson's disease. Biochem Biophys Res Commun 2010;396:152–156.
5. Wakeman DR, Dodiya HB, Kordower JH. Cell transplantation and gene therapy in Parkinson's disease. Mt Sinai J Med 2011;78: 126–158.

DOI: 10.1002/ana.22677

Nonequivalence of Equivalence Methods

Laura S. Boylan, MD,[1,2] and Joshua J. Gagne, PharmD, ScD[3]

Krauss and colleagues reviewed the bioequivalence of generic antiepileptic drugs (AEDs) by analyzing US Food and Drug Administration data for generic approval, using these data to indirectly compare generic–generic bioequivalence.[1] The authors sound a cautionary note regarding generic to generic switching, but do not acknowledge an important limitation to indirect comparisons.

When indirectly comparing 2 independent estimates, the variance of the resulting estimate will always be larger than the variance of each original estimate. That is, the variance of the ratio indirectly comparing 2 generic AEDs (ie, $[SE1^2 + SE2^2]^{1/2}$ from Krauss et al[1]) will always be greater than the variance of each of the individual generic–brand ratios (i.e. $SE1^2$ or $SE2^2$), because the former must account for uncertainty in both ratios being compared. Readers might misconstrue this larger variance as a reflection of nonequivalence between the 2 generics rather than as nonequivalence between direct and indirect comparison methods.

Consider the following scenario. Generic drug A is bioequivalent to a brand name product with an area under the curve $(AUC)_{0-t}$ ratio of 1.0 (90% confidence interval [CI], 0.81–1.23), and generic drug B is bioequivalent to the same brand name product with an AUC_{0-t} ratio of 1.0 (90% CI, 0.81–1.23). The resulting ratio of these ratios is also 1.0, but with a 90% CI of 0.74 to 1.35. Therefore, large maximum limits of 90% CIs, even up to 35% as shown in the authors' Figures 4 and 5, are not unexpected even under perfect bioequivalence or in indirectly comparing batch to batch variability of brand medications.[2] Thus, clinicians concerned about generic AED bioequivalence should be reassured by Krauss et al's results.

Most importantly, the clinical relevance of small variations in bioavailability among generic drugs in epilepsy is unsubstantiated. A recent meta-analysis of randomized studies did not find a difference in seizure outcomes among patients treated with generic AEDs as compared to those treated with