



Remembering that old dogs can still do tricks

More and more we are realizing that we need trials that use hard clinical end points to inform our clinical practice. Several things we used to do based on observational studies have fallen from grace after being evaluated in interventional trials. And faced with the US Food and Drug Administration's mandate to demonstrate clinical impact, pharmaceutical companies can rarely count on using even well-accepted biomarkers instead of clinical outcomes when trying to bring new drugs to market.

This atmosphere often makes us a bit uncomfortable when prescribing older drugs that have passed the test of time and collective anecdotal experience but not rigorous clinical testing. In some cases this is good, and robust evaluation provides greater confidence in our choice of therapy: witness the demise of digoxin for heart failure.

Many older drugs have never been compared with newer drugs in well-designed trials using hard clinical outcomes and likely never will, owing to cost, marketing, and logistic reasons. But sometimes these trials are done, and the results are surprising. For instance, methotrexate in appropriate doses may actually be comparable to newer and far more expensive tumor necrosis factor inhibitors when used to treat rheumatoid arthritis.

Should we be willing to sometimes accept data on surrogate markers (eg, low-density lipoprotein cholesterol levels, blood pressure, hemoglobin A_{1c}) or even extensive clinical experience in the absence of hard outcome data when using older, tried-and-true drugs? Markers can mislead: consider the higher number of deaths recorded in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in the group receiving more aggressive control of their glucose levels.

So we should not be totally sanguine when using older drugs instead of newer ones. But some drugs may have slipped out of our mental formularies yet still have real value in niche or even common settings. Methyldopa remains an effective antihypertensive drug and may be especially useful in peripartum patients. Yet relatively few young physicians know the drug.

And so it may be with chlorthalidone. On page 527 of this issue of the *Journal*, Cooney et al remind us not only that this drug is still around, but that it has proven efficacy and, compared with its more popular cousin hydrochlorothiazide, favorable pharmacokinetic properties such as longer action. Not to mention that it was a comparator drug in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial.

In our current cost-saving environment, we should remember that some old dogs can still do good tricks.

A handwritten signature in black ink that reads "Brian Mandell". The signature is fluid and cursive, with a long horizontal stroke at the end.

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