

The M. Powell Lawton Award Lecture.

Clinical Trials in Late Life: New Science in Old Paradigms*

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Abstract

Purpose. This Lawton Award Lecture addresses the subject of the need to enhance the evidence base in our field in order to influence processes of policy development. Four issues are identified as critical to this: theory-driven targets of public-health significance; use of appropriate and sophisticated methodologies; development of instruments and measures; and conclusions that make a difference. Incentives are discussed with particular attention to regulatory approaches. **Design and Methods.** A broad view of research is taken with examples from studies of Alzheimer disease and depression in late life. **Results.** Areas for new development are identified. **Implications.** New approaches to methodology will enhance our capacity to translate exciting new findings from the basic sciences into the development of therapeutics.

Key words: clinical trials; Alzheimer disease; depression; methodology

Clinical Trials in Late Life: New Science in Old Paradigms

I begin with an extract from a “Serious Adverse Event” report submitted for a participant in an ongoing clinical trial: “An 82 year-old female [resident of an Alzheimer care assisted living facility] was hospitalized for chronic obstructive pulmonary disease (COPD) exacerbation and acute respiratory failure due to COPD exacerbation ... while enrolled in the CATIE trial, a study comparing the effectiveness of antipsychotic medications in patients with Alzheimer disease. The patient started open choice medication, olanzapine on ... Concomitant medications included prednisone, fluticasone, salmeterol, albuterol, and ipratropium for chronic obstructive pulmonary disease, donepezil for Alzheimer disease, potassium chloride for potassium supplement, Caltrate with Vitamin D as a nutritional supplement, furosemide for edema, isosorbide for hypertension, rabeprazole for gastritis, levothyroxine for hypothyroidism, clopidogrel for history of TIA, and tolterodine for incontinence. The patient’s medical history includes transient ischemic attacks (TIA), hypertension, incomplete right bundle branch block, COPD, Alzheimer disease, syncope, hypoxemia, emphysema, gastritis, hypothyroidism and myocardial infarction.” This was her fourth hospitalization in three months (twice for TIAs, once for a urinary tract infection, and the current one for COPD). She was discharged after a hospital stay of four days. The option of discharge to hospice care was

discussed with her daughter; the decision was that she return to assisted living with “more frequent attention from the caretakers there.”

What a story this report tells: the capacity of contemporary health care to address issues of chronic disease, the multiple actions of a dozen different medications, a daughter closely involved in her mother’s care, an assisted living facility developed specifically to care for people with Alzheimer disease. And this only scratches the surface of the issues that are raised by this woman at the end of her life.

I begin with this “case report” for many reasons, but principally as a reminder that health policy, and the research that informs that policy and provides the evidence base for its development, must address the issues that are raised by this woman’s needs. Stanley J. (Steve) Brody, used to say that health policy was easy if someone thinks that all that it involves is moving boxes and arrows on a piece of paper. The trouble is, that health care is not just boxes and arrows. Health care is the woman in this report: it is people and families, the clinicians that care for and about them, and the administrators and policy makers that create the context in which that care is provided. Our challenge in research is providing the evidence that can guide, or at least inform, the development of those policies.

The Gerontological Society of America (GSA) recognizes that challenge. Our mission in the GSA is to promote the conduct of multi- and interdisciplinary research in aging by expanding the quantity of and improving the quality of gerontological research, and by increasing its funding resources; and to disseminate gerontological research knowledge to researchers, to practitioners, and to decision and opinion makers (<http://www.geron.org/mission.htm>). This dual mission has fundamentally shaped the nature and direction of the work that I am honored to present in this lecture. And by doing so, I hope, in a small way, to pay respect to the legacy of M. Powell Lawton. For over thirty years Powell was my mentor, teacher, colleague, and friend. In a very real sense, his influence shaped the direction of my entire career and the careers of many others of my generation.

Since our challenge is to provide evidence that can be used to guide or inform policy development, we must look at what we study, how we study it, and what we do with the results. In particular, there are four aspects of the issue of evidence that I intend to explore. By doing so, I hope to identify some considerable strengths in our field but also to specify areas and issues in need of attention and development. I will emphasize four broad areas:

- Identification of theory-driven targets of public health significance
- Use of appropriate and sophisticated methodologies
- Development of instruments and measures
- Conclusions that make a difference

Targets of significance

As part of a volume that, in retrospect, serves as a Festschrift to Powell Lawton (Lebowitz, 2000b), I linked the emerging “public health” model of treatment research to many of the themes that had been articulated in Lawton’s work. I argued that mainstream mental health research was moving away from short-term symptom management studies in highly selected populations. Research in young and mid-life adult populations was beginning to address problems of long-term functional outcomes in heterogeneous and representative populations. I concluded that the models that Powell Lawton had developed in gerontology and geriatrics were now being exported across the life-course. In particular, attention to comorbidity, function, disability, and quality of life in settings of general health care, social service, and long-term care were now the standard against which new approaches were being developed in research with early and midlife

populations. Looking back, many will recall the discussions in the 1970s and 80s about the need to “gerontologize” training and practice in health and social services. How far we have traveled from trying to get attention to our issues to, now, providing leadership in conceptual and methodological development.

In the description of the public-health approach to treatment research I used the example of Alzheimer disease to illustrate the point. For reasons having to do more with academic politics and strategies to optimize reimbursement for care, the prevailing sense was that Alzheimer disease should be seen as strictly a cognitive disorder. Any other symptoms or dysfunctions were regarded as secondary and incidental to the core cognitive deficit. My main point in the paper involved arguing the somewhat unusual case that we needed to get back to Alzheimer’s original conceptualization, specifically that this disease was multidimensional, with dysfunction not only of cognition but also of mood, thinking, and behavior.

Much has happened since then to establish this multidimensional principle as the standard in the field. This view has guided a new generation of treatment development studies.

And once again, gerontology and geriatrics has led the way—this time, for a whole new

approach to the targets of treatment. The issue can be posed as follows: what is it that we treat when we develop treatments for brain disorders?

First and foremost, we are dealing with a very complex system, and the complexity seems to be increasing as our knowledge increases. The scale of the central nervous system (CNS) goes from 10^2 (the number of neurotransmitters) to 10^{12} (the number of synapses). In addition, data from imaging and from neuropsychology show that the pathology associated with brain disorders is widely distributed through the CNS. Genetic studies have shown that many, if not most brain disorders are polygenetic with multiple biochemical pathways that may contribute to the expression of a single disease. Environmental factors may contribute as much as half the variance in disease expression. Coupled with a system of diagnostic classification that is often ambiguous and incomplete, our challenge in treatment development is formidable indeed (Kennedy, et al., 2003; Merikangas & Risch, 2003).

Although we like to think that we treat diseases, for the time being at least, it is symptoms, and occasionally syndromes that are treated. With Alzheimer disease, research in neuropathology, brain imaging, and neuropsychology all provided the basis

for what developed as the first instance in CNS of regulatory and policy recognition that development of syndromal indications for treatment is appropriate and necessary.

In the USA, the certification of biological treatment approaches is regulated by the Food and Drug Administration (FDA). The FDA has identified a number of conditions that must be satisfied in order for a treatment to be approvable (Laughren, 2001), i.e. before evaluating the proposed treatment for safety and efficacy. Two different approaches are possible.

One approach takes the route of demonstrating that the proposed treatment is specific to the clinical entity under consideration but not “pseudospecific”. That is, there cannot be a claim of uniqueness for a particular clinical entity in the absence of data supporting such a claim. There must be general acceptance of the treatment target in the expert community, identification of a reasonably homogeneous patient population, and, ideally, some understanding of etio/pathophysiologic mechanisms. In the case of Alzheimer disease this came from a variety of sources in basic and clinical research (Lebowitz 2000b). If those criteria are satisfied then there is need for specific, operationally definable, diagnostic criteria. Along with the general categories of Alzheimer disease and Mild Cognitive Impairment (MCI), specific diagnostic criteria have been developed

for three syndromes in Alzheimer disease: psychosis (Jeste & Finkel, 2000); depression (Olin et al., 2002); and sleep disturbance (Yesavage et al., 2003).

A second approach to gaining approval for a syndromal treatment indication is to demonstrate that the syndrome is similar across a wide variety of illnesses. Pain and fever are two such generalized examples; “agitation” seems to fall into this category as well. By establishing the principal the syndromal indications are achievable in Alzheimer disease, basic and translational research in the field has established a new context for of treatment development studies (DeDeyn, et al., 1999; Katz et al., 1999; Lyketsos et al., 2003; Schneider, et al., 2003a; Street et al., 2000).

In addition to the obvious clinical benefit of having treatment options available for a range of severely disabling conditions, a major contribution of this syndromic approach is that research in geriatrics has once again paved the way for developments in the rest of the life course. The regulatory approvals of the atypical antipsychotic clozapine as a treatment for suicidality in schizophrenia and of injectible antipsychotics for the treatment of agitation in schizophrenia or mania are derived directly from the concept of syndromal indications in Alzheimer disease. A renewal of interest in the enhancement of cognitive function in adults with schizophrenia and in the treatment of depression in

Parkinson's disease have been stimulated by the acceptance of syndrome-based indications in Alzheimer disease. The public health implications of these developments are profound and important.

Appropriate Methodologies

In order for our data to contribute to the policy process, the research upon which it is based must meet the highest standards of methodological excellence. My work has been focused on therapeutics and clinical trials, so let us examine the use of clinical trials data to guide what has come to be called evidence-base practice. In other words, how good are the treatment approaches we use?

The evidence from clinical trials does not provide a definitive answer to that question. Why? It could be that our treatments are not very good. Or it could mean that we don't study them right.

Most controlled trials of antidepressant medications fail to demonstrate superiority of active treatment over placebo both in mid-life (Khan, et al., 2003) and in late-life (e.g. Roose, 2002). And of those trials that do identify positive treatment effects, the size of

that effect is so small (Schneider, et al., 2003b; Tollefson, et al., 1995; Williams, et al., 2000) or the intervention so complex (Unutzer, et al., 2002) that any reasonable person would avoid these treatments whenever possible. Large placebo effects have been observed in trials of new agents to treat depression or the psychotic symptoms of Alzheimer disease. At the same time, paradoxically, we know that millions of people are treated for these disorders worldwide and that many of them derive substantial benefit from treatment. How do we account for the difference? How is it that treatments work very differently in actual practice than they do in controlled clinical trials?

I believe that a major source of the difference lies in the fact that the methods we use to study new approaches to treatment in human clinical trials were set for the most part in the 1940s and 1950s with the first modern randomized controlled trial, the Medical Research Council trial of streptomycin (MRC, 1948). Having frozen our methodology and not taken advantage of developments in contemporary statistical science has had a downside, however. Nearly everything we do in clinical trials minimizes treatment response, enhances placebo response, and, in the case of combination treatment studies, distorts the value of certain active comparators. There are many factors that contribute to this. I will focus on three of them: patient selection; study operations; and statistical analysis.

Patient selection. Subject selection often is limited (Anand et al., 2003) by censoring the severity distribution through entry criteria where exclusions often require elimination of patients that are suicidal, psychotic, and with a variety of common comorbidities such as physical illness, substance abuse, or personality disorder. Since these are typically associated with severity, elimination leads to preferential recruitment of less severely ill subjects (Schneider, et al., 1997) or otherwise non-representative patient samples. This is not restricted to geriatrics, but is generally true in all registration-oriented studies in mental disorders (Licht, 2002; Robinson, et al., 1996; Zimmerman, et al., 2002). Similarly, many studies have long no-treatment periods for observation and diagnostic purposes. Clinicians are not likely to withhold treatment from severely ill patients in whom immediate treatment is seen as an absolute necessity. Thus, only those patients that can tolerate a long no-treatment period are recruited. These are likely to be less severely ill (DeDeyn, et al., 1999; Katz, et al, 1999; Street, et al., 2000). It has long been observed that severity and placebo response are inversely related.

If advertising is used as the primary source of recruitment, a group of high likelihood placebo responders, the “worried well”, are often the ones recruited. If, on the other hand, is largely from active clinic or practice populations, there is likely to be preferential

treatment of non-responders under the justification that it is inappropriate to “rock the boat” for patients that are doing well by switching to a new treatment.

The patients recruited for typical studies are very likely to respond to placebo or do not respond to anything—hardly an ideal laboratory for the testing of a new approach to treatment.

Study operations. There seems to be a general notion that treatment studies are “easy”. Methods are seen as straightforward: all that is necessary is recruitment, exposure of some participants to one treatment option and some participants to a different one, and followup. Even if studies were as easy as this to design, and they are not, they are very difficult to actually carry out (see, for example, Friedman, et al., 1998). Many studies fail not because they are poorly conceived but because of they are poorly organized and run.

In an addition to overall problems of operations, there are several specific issues that compromise study outcomes. For example, in large, multiple site studies, recruitment is often set as a horse-race with enrollment concluded when the overall study sample is achieved. Payment to sites is largely on a per-patient basis. Therefore, as the study recruitment goal appears closer, there is a financial incentive to enroll subjects while

enrollment is still possible. Over time, that could lead to a drift in criteria: mild symptoms are seen as more serious, and borderline eligibility gets to be considered acceptable. This erosion of severity promotes recruitment of those with milder severity who, as described above, are more likely to respond to placebo.

In combination treatment studies, that is, those that include both a pharmacologic and a non-pharmacologic approach, operational concerns may minimize differences between pharmacological and psychosocial treatments. Typically, the approach to pharmacotherapy is rigid with fixed dosing and short duration—an approach uncharacteristic of clinical practice. Clinicians in the pharmacotherapy arm must behave robotically and in a manner unlike the way they generally work. Training and supervision are minimal. Those doing the psychosocial treatment, on the other hand, are typically highly selected, well paid, well trained, and closely supervised. We therefore commonly encounter trials in which (expertly done) psychotherapy beats (poorly done) pharmacotherapy. In these studies, however, it is very difficult to separate the operational aspects from the true clinical effect of the different treatment approaches (Thompson, et al., 2001).

Statistical Analysis. The preferred approaches to statistical analysis of trials data, such as “intent to treat” and “last observation carried forward” may reward placebo response. Newer approaches such as mixed-effects modeling and survival models may provide crisper alternatives for the identification of treatment effects. And, of course, statisticians continually remind us that effect size estimation, not statistical significance, should be the criterion applied to all trials.

Clinical trials often fail because we feel constrained to follow the classic approaches to clinical trials methodology. New science and the new treatments derived from it should be assessed with a methodology that is appropriate and built upon the best of our current knowledge. As we develop new treatment approaches for major disorders (see, for example, Holden, 2003), there is a pressing need to reengineer the standard approaches to clinical trials in the mental disorders.

More than ever before we now have the opportunity to revolutionize treatment discovery for the mental illnesses. With advances in cognitive and behavioral science, molecular biology, genomics, proteomics, bioinformatics, and automation we have the tools we need to move to a whole new approach to treatment development (Collins, 1999; McKusick 2001; Subramanian et al., 2001). Using genomics and proteomics it will be

possible to redefine phenotypes (Merikangas & Risch, 2003) by creating mechanism-based classifications of clinical patient populations to use in the development of therapeutic or prophylactic interventions. All this will move us from an approach based on serendipity to one based on rationality (Peltonen & McKusick, 2001). The therapeutics of the future will be expected to identify specific targets with minimal side effects in genetically defined clinical populations (Collins & Guttmacher, 2001).

We also need to remember that discovery and development are the beginning and mid-point of treatment development, not the end. Traditional models have limited generalizability, restricted outcome measures, and leave substantial amounts of non-response, residual symptomatology and associated disability (Lebowitz, 2000a). New pragmatic or practical trials, based on approaches articulated by Peto and colleagues (Yusef et al., 1984) and Tunis and colleagues (2003), are expanding our vision with respect to treatment assessment in our field.

Instruments and Measures

A highlight of Powell Lawton's contribution to our field was the development and use of new measures: approaches to functional assessment, instrumental activities of daily

living, quality of life, daily affect. We continue to have great need for better instruments to use as outcome measures in clinical trials. In psychiatry trials in general, and in depression trials in particular, there is a tradition of using too many measures, most of which are rating scales or self-report forms of dubious validity and notorious unreliability.

Measures are selected because they have worked in the past and are therefore uninformed by contemporary science and knowledge of etiology or pathophysiology. This is important because treatments may be having effects that our standard measures are incapable of capturing. The standard outcome measure used in depression trials, the Hamilton Rating Scale for Depression (Ham-D), was developed nearly a half-century ago to assess the impact of the then new class of antidepressants, the tricyclics, on severely depressed inpatients (Hamilton, 1960).

Other areas of health take other approaches that we might adapt. In the 2000 Festschrift (Lebowitz 2000b) I identified several dimensions that held out the possibility of a new look at outcomes: institutionalization, morbidity, mortality, disability, resource use, quality of life, family burden. I cited a few examples of these in that 2000 paper. There is need to go beyond the discrete measure, however, to develop composite, event-based

measures for use in mental health. This type of measurement was developed for use in cardiovascular trials (major adverse cardiac events, MACE). There has been one example used in schizophrenia: a composite measure of suicidality in people with schizophrenia that was used in the trial of clozapine (Meltzer, et al., 2003). We need to have more. I have proposed, not entirely with tongue-in-cheek, that, notwithstanding the psychodynamic interpretation, we develop a measure for depression using suicide attempts, hospitalization, needs for rescue treatment, and significant exacerbation of symptoms. Such a measure, consolidating a variety of major adverse depression related events, would, unfortunately, be known as MADRE.

Conclusions that Make a Difference

Targets, methods, and instruments: all partial answers to a single underlying question-- what special considerations are necessary in the design of a geriatric protocol? That is, how do we establish a general understanding of what would constitute a geriatric protocol to assess the safety and efficacy of new treatments (Arean et al., 2003; Lebowitz & Harris, 2000; Norquist et al., 1999). A proper geriatric protocol is not simply an established “adult” protocol with the age range extended into late life. In studies using drugs, the dosing and duration of treatment must reflect the potential effects of age-

related changes in pharmacokinetics and drug metabolism and the effects of comorbid conditions and their treatments. In studies using non-pharmacologic approaches, the type of treatment selected for study must reflect the social, cultural, and clinical realities of late life. In all cases, restrictive exclusion criteria should be minimized in order to optimize generalizability, and both symptomatic and functional outcomes should be assessed.

There is more than a purely scientific context for this set of issues. In his 1986 Donald P. Kent Memorial Lecture, Steve Brody (1987) wisely observed that public policy emerges and is guided by “the felt necessity of the time”. One of the felt necessities of our time is the need to address the economics of pharmaceuticals for older people. As I write this, a prescription drug benefit in Medicare is an issue of major prominence in policy development. There seems to be general agreement regarding public funding of many drugs for many older people. It seems to be a question of “when” and “how”, no longer a question of “whether”. It seems logical that at some point in this process of policy development there will be questions raised about the adequacy of the evidence upon which to base drug prescribing for participants in the Medicare program. This evidence needs to come from the kind of studies that I have been describing.

What are the incentives to produce this evidence? There have been two approaches to improving evidence of the safety and efficacy of drugs used by older people. It is beyond the scope of this paper to describe these in detail, and I will use very broad brushstrokes.

The earliest of these, developed by the International Conference on Harmonization (an international body representing drug regulatory authorities in North America, the European Union, and Japan) (1994), establishes the principle that drugs should be studied in all appropriate age groups and be reasonably representative of potential consumers. This principle has never been fully implemented.

A second approach was developed in 2001 by the Food and Drug Administration (FDA) in the US establishes a “Geriatric Use” section of drug labeling with information coming from any source, including spontaneous reporting, not restricted to controlled clinical trials. The variability in the information available under this very open policy has limited the impact of this guidance.

One highly successful approach to generating specific evidence regarding treatments is from the area of pediatrics. Since 1997 in the US there has been an incentive, in the form of an additional six months of patent protection, for those drugs that are specifically

studied in children. These studies must be requested by the FDA, which, as of October 2003 has requested nearly 300 studies and has approved patent extension for 84 drugs (data accessed at <http://www.fda.gov/cder/pediatric/index.htm#pedexcl-stats> on 10/31/2003). Concerns with the selection of drugs and the overall cost impact have been raised in the context of this incentives-based approach, but no one can dispute the public health value of the program. Indeed, renewal of the legislation authorizing this program was approved unanimously by the US Senate in October 2001. Many of us believe that this type of approach needs to be examined as a way to increase the base of our knowledge in geriatrics.

“Older persons need a dream, not only a memory.” Rabbi Abraham Joshua Heschel taught us this at the 1961 White House Conference on Aging. Arthur S. Flemming inspired us with those same words 34 years later, at the 1995 White House Conference (Flemming, 1995). Much remains to be done to fulfill this charge. This spirit has guided the line of work that Powell Lawton established, that those of my generation have been pursuing, and that I have had the honor to present in the M. Powell Lawton award lecture.

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