A public health approach to clinical therapeutics in psychiatry: directions for new research

Barry D. Lebowitz, PhD

Treatment works. A generation of research has led to this inescapable conclusion. A vast body of literature including complete textbooks, chapters, and aggressive public and professional education campaigns fully explicate this positive message. Yet, among ourselves, we are generally less positive about the impact of our treatments on our patients’ lives. We will agree that most patients do pretty well most of the time on most treatments. But we will also agree that this is not nearly good enough and much more needs to be learned about how treatments work.

What, in particular, don’t we know as well as we would like? Why do treatments rarely work as well in practice as they do in clinical trials? Why are the approaches to treatment that are studied in research settings rarely the ones that are used in practice? Does treatment enhance functioning? Does early treatment predict a more favorable response? How can we keep people well once they have been made well? What approaches should be used for the treatment-resistant patient?

These are the sorts of questions that are raised within the context of what has been called a public health model of treatment. These are questions we cannot yet answer as well as we would like, however, largely because the direction and culture of treatment research has been determined by a more narrowly defined regulatory model. This regulatory model has been the dominant force shaping treatment research in the past and we will explore some of its limitations below.

Traditional (regulatory) clinical trials: strengths and weaknesses

Most treatment studies are done with a very specific purpose in mind: to gain approval or acceptance of a particular therapeutic modality. These studies are usually referred to drug approval and registration to a more inclusive public health model. Thus, whereas regulatory antidementia trials will exclude patients with psychiatric or neurologic symptoms or substance abuse and require them to be physically healthy and living with a caregiver, ie, 90% of the presenting Alzheimer population, the public health model promises to improve patient care by addressing the types of practical questions and functional outcomes typically the concern of clinicians: Does treatment enhance function? How can we keep people well once they have been made well? Why do treatments not work as well in practice as in clinical trials? Public health studies are conducted in the world of actual practice with time-pressed clinicians taking care of large numbers of patients with uncertain clinical presentations, complex comorbidities, and varying degrees of interference with ideal levels of compliance. The exclusive focus on symptoms is expanded to include outcomes related to issues of function, disability, morbidity, mortality, resource use, and quality of life. Highly controlled efficacy research is still needed to establish treatment merit, but efficacy now marks only the beginning of the process of inquiry.
to as trials to establish efficacy. This type of consideration is appropriately referred to as a “regulatory” one. Research following the regulatory model is specifically geared to the legal requirements of drug approval and registration. Although there is no equivalent to the Food and Drug Administration (FDA) for psychotherapy, the methodology of the regulatory model has been adopted in that field as well. In order to establish efficacy, it is essential that pure disease entities are isolated. This has led to the practice of eliminating from clinical trials all patients with comorbid illnesses, coexisting conditions, and even potentially compromising psychosocial or environmental characteristics. Dimensions of outcome are limited to the direct symptomatic measures of that disease. Observation periods are, typically, very short. In order to prevent administrative or delivery problems from masking the effect of the treatment, clinicians are carefully selected and trained. Intrusions such as the administrative requirements of a health care plan or third party payer are minimized, and the treatment is provided in optimal form, often in an academic health center. Specific measures are taken to ensure compliance of the clinician with the protocol and adherence of the patient with the procedures and treatments. Formally, efficacy studies define optimal treatment outcomes for narrowly selected patients treated under rigidly controlled and ideal conditions. With a primary focus on symptoms, the assessment of efficacy is based upon the degree to which the level of symptomatology is reduced or eliminated.6 In an efficacy trial, treatment is provided by specially selected and trained clinicians who provide optimal treatment and expend substantial resources to ensure compliance and minimize drop out.

Research supported for commercial purposes, particularly that supported by the drug companies themselves, has, of necessity, conformed to the regulatory model. This is the case regardless of whether the site of the study is an academic health center or a community treatment facility, and regardless of whether the coordination of the study is done directly by the sponsor or by an intermediary (contract research organization, or CRO). It is worth noting that those doing clinical psychotherapeutic or behavioral research have not (yet) adopted this CRO type of arrangement. The regulatory model has also been carried over into research that has no industrial sponsorship, even to research on mental disorders that has been directed to government agencies or foundations. In a treatment study driven by a regulatory model of investigation, there is no minimum effect size or minimum proportion of responders necessary. In addition, there is no requirement that the subject population be representative of the kind of patient seen in actual practice. As such, a trial done in accordance with the regulatory model represents only the beginning of a process of clinical development. Efficacy studies define optimal treatment outcomes for narrowly selected patients treated under rigidly controlled and ideal conditions. The classic efficacy trial is used to define the gold standard of the best outcome under ideal circumstances. Because of the tight standard of control required in efficacy studies, the policy and practice relevance of these trials will always be limited.9

The clinical trials of cognitive enhancers provide a useful example of the differences between regulatory and public health research. The trials of cognitive enhancers seek to show slowing or reversal of the progression of Alzheimer’s disease or to demonstrate improved management of the symptoms of the disease. These trials typically attempt to show that the course of a progressive disease has been modified. The design of such trials involves great complexities even under optimal conditions.9 In an effort to demonstrate efficacy within the regulatory model, current clinical trials involving antidementia compounds typically exclude any patient with psychiatric or neurologic symptoms or substance abuse, and require the patient to be generally physically healthy and living with a caregiver. Schneider et al10 applied these criteria to a large, state-wide database in California and excluded all but 10% of patients. The resulting sample was younger, less severely ill, more highly educated, and more likely to be white and with higher incomes than the population as a whole. These sorts of data provide little guidance to the patient, family, or clinician in the selection of treatment approaches. In fact, there is a small but growing literature on issues relating to subject selection in clinical trials.11 In schizophrenia, for example, subjects tend to be younger than the general clinical population and are more likely to be male and part of an ethnic minority.12 In the Treatment Strategies in Schizophrenia (TSS) study, fewer than 10% of those screened were actually enrolled in the study.12 The story is much the same in bipolar illness. In general, subjects enrolled in studies tend to have been ill for a very long time—15 years in bipolar trials13—and are unstable or unsatisfied with their current treatment. Even in studies attempting to recruit first-episode patients, the period of undetected or untreated illness exceeds 3 years.14 Age itself is a common concern, with many studies having an arbitrary age cutoff of 55 or 60 years. Even “geriatric” studies...
have been restricted, for all intents and purposes, to the “young-old” population of patients in their sixties. Few older patients have ever been studied, despite the clear impact of advanced age on pharmacokinetics, dynamics, and drug metabolism and on treatment response. In general, the rigid exclusions of most regulatory-oriented clinical trials have significantly distorted the conclusions of these studies.

**Public health model intervention studies**

Studies that are informed by a public health model are often called “effectiveness” studies. We avoid use of that term since it seems to convey multiple and conflicting meanings in different audiences. Public health studies bring us into the world of actual practice with time-pressured clinicians taking care of large numbers of patients with uncertain clinical presentations, complex comorbidities, and varying degrees of interference with ideal levels of compliance. The exclusive focus on symptomatology is expanded to include outcomes related to issues of function, disability, morbidity, mortality, resource use, and quality of life. The classic public health trial is used to assess the expected outcome under usual circumstances of practice.

In contrast to the elegantly crafted efficacy trial, a public health trial must be bigger in size, simpler in design, broader in terms of inclusions and narrower in terms of exclusions, and more representative with respect to settings of care. These settings will not be limited to academic health centers or tertiary care institutions, but will include primary care, community settings, and long-term care institutions. Unlike efficacy trials, where specially trained clinicians carry out state-of-the-art assessment and treatment, public health trials are carried out in settings of usual practice where there is a broad and variable range of clinician expertise and experience with the disorder under study. Outcome measures will necessarily extend beyond symptomatology to include function, disability, morbidity, mortality, health care and other resource use, family burden, institutionalization, and quality of life. Public health studies are not simply secondary analyses of administrative data collected in large and naturalistic databases, but are treatment trials that are broadly representative of clinical, family, and organizational factors.

**Types of intervention research**

We begin with the assumption that the mental disorders of late life are chronic, recurring conditions. Within this broad perspective, three types of studies would seem to be appropriate. First are treatment trials including both short-term and long-term studies directed toward management of symptoms, optimization of function, and minimization of disability. Treatment trials of this kind are common and well recognized in the field. The conceptualization of the nature of treatment response is broader in public health trials than in regulatory trials. Rather than focusing exclusively on response as a dichotomous variable, ie, responder or nonresponder, a public health approach requires in addition that attention be paid to speed of response, completeness of response, and durability of response.

An intervention directed at the speed of response fits within an overall conceptualization of treatment. The question is how can we accelerate the response to treatment and how early in the treatment process can we know when an approach to treatment is likely to fail? A related question concerns the management of treatment-resistant cases. Regardless of how treatment response is defined, we know that invariably a subset of patients show incomplete responses or nonresponse to any given treatment intervention. Under the regulatory model, the management of nonresponders and partial responders receives relatively little attention. Yet treatment-resistant patients make up a significant portion of actual clinical practice and they account for a major share of the mortality, morbidity, and cost of mental illness. Therefore, a public health orientation requires that the management of treatment resistance be a priority for investigation.

An intervention directed at the completeness of response is considered rehabilitative. The question is how well is well and can we improve the nature of response by targeting interventions to reduce residual symptomatology posttreatment? A rehabilitative strategy might entail augmentation with a new pharmacologic or psychotherapeutic agent or some significant alteration in lifestyles and circumstance.

An intervention directed at durability of response is considered preventive. The question is once well, how can we stay well and can we reduce the risk of relapse (of the same episode) or recurrence (of a new episode) through some longer term approaches to treatment? Interventions are also preventive if they target the excessive levels of disability that often characterize the mental disorders of older people. As we learn more about the risk
factors, etiology, and pathophysiology of mental disorders in late life, it is conceivable that preventive interventions could be directed toward delaying the onset of disease or even preventing the onset entirely.\textsuperscript{20}

\section*{Infrastructure considerations for public health model studies}

In order to carry out such studies, whether they are treatment studies, preventive interventions, or rehabilitative interventions, we need to identify the structural barriers in the ways in which research is organized and to innovate approaches to address these barriers. Researchers and their laboratories are largely based in academic health centers. The role of the academic health center is being redefined in the context of health care system reorganization, and access to patients has become problematic. Patient-oriented research is seen as a particularly fragile enterprise at this point in time.\textsuperscript{21,22} There are important opportunities emerging, however. Many academic health centers are part of clinical systems that include community hospitals, primary care and specialty care office practices, and capitated contracts. The nonacademic settings of these large networks are where the majority of patients are located. The new challenge for the field is how to turn these clinical and administrative networks into research networks for the development and management of intervention trials. At the same time, the parallel challenge is how to identify the critical elements of academically based protocols and paradigms, and adapt them for use in the broader community. Advancement for academic investigators is based on research productivity, usually measured by significant publications and success in developing extramural funding. Large-scale, longitudinal, public-health-oriented studies typically have a very long period of time before important publications are developed, and they usually involve the participation of a large number of investigators. Individual intellectual contributions can be difficult to assess in such projects. If there is a commitment to developing this type of research, the challenge for the field is how to adapt promotion and tenure policies to this situation so as to properly recognize individual contributions.

Similarly, much of the training of new investigators is based upon a model of individual scientific activity: the independent investigator directing a small group of junior colleagues, fellows, students, and technicians. Training typically does not prepare investigators for participation in large-scale endeavors. Nor are there established training pathways into some of the newer roles in large-scale studies, database management, clinical coordination, site management, etc.

\section*{Issues in priority setting}

Determination of priorities within this broad panorama of intervention research is always the result of the complex interaction between public health need and scientific opportunity. However, this is not as straightforward as it appears. We can estimate public health need in many ways. Death, disability, and societal and family burden have each been proposed as the sole criterion for policy determination. For example, in the influential text \textit{The Global Burden of Disease},\textsuperscript{23} major depression, bipolar disorder, schizophrenia, and obsessive compulsive disorder are all included on the list of the 10 leading causes of disability worldwide. In fact, major depression is identified as the leading cause of disability. On the other hand, in that same study, no mental disorder is included as a leading cause of death worldwide. The identification of significant areas of scientific opportunity is equally problematic, with investigators from different fields advocating on behalf of substantial increases in the investment in their particular areas of interest. The National Advisory Mental Health Council, with the legislative mandate to guide policy development and program support, has become a valuable sounding board for the identification of promising scientific opportunities. This Council has produced recent reports on genetics research,\textsuperscript{24} prevention research,\textsuperscript{25} and the interface of clinical trials and mental health services research.\textsuperscript{26} Priority setting must be part of a continuing process of programmatic adjustment, readjustment, and redirection in the field. New treatments must be developed as our knowledge base of basic and clinical neuroscience and behavioral science expands. Established treatment approaches must be fine-tuned in accordance with the needs of patient populations and the settings in which they receive care. Research must catch up with practice and evaluate the many common approaches to treatment that have developed without a firm base of research. Here we include such approaches as continuation and maintenance electroconvulsive therapy, reduction or taper strategies, treatment algorithms or decision trees for patients with treatment refractory illness, and unusual treatments.
such as methylphenidate for minor depression. A wealth of potentially promising treatment approaches currently exists in the form of case reports, uncontrolled studies, letters to the editor, and Internet postings. A major goal for the public health enterprise will be to organize and systematically study these interventions and identify those which are clinically valuable and those which are not. As part of a public health mission, we must also attend to issues of safety and consumer protection. For example, the widespread use of over-the-counter, unregulated treatments needs to be carefully examined for possible benefit and for potential harm. Use of complementary and alternative approaches is very high.\(^{27,28}\) Even in patients volunteering for participation in clinical drug trials, use of herbal medications is substantial; in a series of 150 such subjects, Emmanuel and colleagues\(^{29}\) report that 56% have used herbs in the last month. It is therefore incumbent upon us to evaluate these treatments, including natural products such as St John’s Wort or kava, psychophysiologic approaches such as eye movement desensitization and reprocessing (EMDR), and somatic approaches such as acupuncture, if for no other reason than that our patients are using these in large, uncontrolled, natural experiments.

A final priority must be dissemination. Our patients are not helped by treatments that are available in only in scientific journals. A recent example highlights the problem. Lehman and Steinwachs\(^{30}\) report that fewer than half the patients with schizophrenia in the United States received a level of care that was consistent with the current state of the art. This is an important finding that cannot be ignored. As a field we must take on the challenge of translating our research into practice and placing the most powerful clinical tools in the hands of patients, their families, and the clinicians that care of them.

**Conclusion**

The mental health field is significantly altering the culture of treatment research by moving from a narrowly defined regulatory model to a more inclusive public health model. This new approach to intervention promises to improve patient care by addressing the types of practical questions and functional outcomes that are typically brought to the attention of clinicians. This new generation of research is directed toward defining standards of appropriate and cost-effective treatment for the diverse population of patients seen in all health care settings. This should not be taken to indicate that there is no place for the highly controlled efficacy research needed to establish that a treatment has merit. But rather it is now the case that efficacy is the beginning of a process of inquiry and not the end. The interdependence of challenge and opportunity, often used as a cliché, should be considered real and entirely appropriate in this instance. The challenge to all of us as patients, clinicians, scientists, or educators is great. We are all having to learn to do new things. At the same time, there is a wonderful opportunity to have a significant impact on improving patient care. This opportunity is too good to miss.

**REFERENCES**

1. Geriatric Psychiatry Alliance. Depression in Late Life: Not a Natural Part of Aging. Bethesda, Md: American Association for Geriatric Psychiatry; 1997.

2. Nathan PE, Gorman JM, eds. A Guide to Treatments that Work. New York, NY: Oxford University Press; 1998:270-287.

3. Salzman C, ed. Clinical Geriatric Psychopharmacology. 3rd edition. Baltimore, Md: Williams and Wilkins; 1998.

4. Norquist G, Lebowitz B, Hyman S. Expanding the frontier of treatment research. Prevention Treatment. 1999;2: Article 0001a. Available at http://www.journals.apa.org/preventionvolume2/pre0020001a.html. Accessed 23 October 2000.

5. Leber PD, Davis CS. Threats to the validity of clinical trials employing enrichment strategies for sample selection. Control Clin Trials. 1998;19:178-187.

6. Scott JD. Hypothesis generating research: the role of medical treatment effectiveness research in hypothesis generation. In: Wenger NK, ed. Hypothesis generating research. In: Geriatric Psychiatry Alliance. Depression in Late Life: Not a Natural Part of Aging. Bethesda, Md: American Association for Geriatric Psychiatry; 1997.

7. Lohr K. Outcome measurement: concepts and questions. Inquiry. 1988;8:37-50.

8. Wells KB, Sturm R, Sherbourne CD, Meredith LS. Caring for Depression. Cambridge, Mass: Harvard University Press; 1996.

9. Leber PD. Observations and suggestions on antidepressant drug development. Alzheimer Dis Assoc Disord. 1996;10:31-35.

10. Schneider LS, Olin JT, Lyness SA, Chui HC. Elibility of Alzheimer’s disease clinic patients for clinical trials. J Am Geriatr Soc. 1997;45:1-6.

11. Rapaport MH, Zisook S, Frevert T, et al. A comparison of descriptive variables for clinical patients and symptomatic volunteers with depressive disorders. J Clin Psychopharmacol. 1996;16:242-246.

12. Robinson D, Woerner MG, Pollock S, Lerner G. Subject selection biases in clinical trials: data from a multicenter schizophrenia treatment study. J Clin Psychopharmacol. 1996;16:170-176.

13. Bowden CL, Calabrese JR, Wallin BA, et al. Illness characteristics of patients and their response from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry. 1999;156:544-549.

14. Robinson DG, Woerner MG, Alvir JM, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry. 1999;156:544-549.

15. Salzman C, Schneider LS, Lebowitz BD. Antidepressant treatment of very old patients. Am J Geriatr Psychiatry. 1993;1:21-29.

16. Von Moltke LL, Abernethy DR, Greenblatt DJ. Kinetics and dynamics of psychotropic drugs in the elderly. In: Salzman C, ed. Clinical Geriatric Psychopharmacology. 3rd edition. Baltimore, Md: Williams and Wilkins; 1998.

17. Reynolds CF, Frank E, Dew MA, et al. The challenge of treatment in 70+ year olds with major depression: excellent short-term but brittle long-term response. Am J Geriatr Psychiatry. 1999;7:64-69.

18. DeFries GH. Measuring the effectiveness of medical interventions: new expectations of health services research. Health Serv Res. 1990;25:691-695.

19. Dickey B, Wagenaar H. Evaluating health status. In: Sederer LI, Dickey B, eds. Outcomes Assessment in Clinical Practice. Baltimore, Md: Williams and Wilkins; 1996:55-60.

20. Lebowitz BD, Pearson JL. Intervention research in psychosis: prevention trials. Schizophr Bull. 2000;26:543-549.

21. Thompson JN, Moskowitz J. Preventing the extinction of the clinical research ecosystem. JAMA. 1997;278:241-245.
Una aproximación de salud pública a las terapias clínicas en psiquiatría: direcciones para nuevas investigaciones

El campo de la salud mental está transformando la cultura de la investigación terapéutica al movilizarse desde un estrecho modelo regulatorio orientado a la aprobación y registro de medicamentos hacia un modelo de salud pública más inclusivo. Así mientras los ensayos antidemencia regulados excluirán pacientes con síntomas psiquiátricos, neurológicos o con abuso de sustancias y requieren que ellos estén físicamente sanos y que vivan con un cuidador, es decir, el 90% de la población que presenta Enfermedad de Alzheimer, el modelo de salud pública promueve mejorar el cuidado del paciente señalando los tipos de preguntas prácticas y evoluciones funcionales que típicamente interesan a los clínicos: ¿El tratamiento mejora la función? ¿Cómo podemos mantener bien a las personas una vez que ellas se han recuperado? ¿Por qué los tratamientos no resultan efectivos en la práctica como lo hacen en los ensayos clínicos? Los estudios de salud pública son conducidos en la práctica mundial actual por clínicos presionados por el tiempo, quienes cuidan de un gran número de pacientes con cuadros clínicos poco precisos, comorbilidades complejas y diversos grados de interferencia con los niveles ideales de adherencia. El foco exclusivo de síntomas se expande para incluir evoluciones relacionadas con temas de función, incapacidad, morbilidad, mortalidad, uso de recursos y calidad de vida. La investigación de la eficacia altamente controlada todavía es necesaria para establecer el valor de un tratamiento, pero la eficacia marca por ahora sólo el comienzo del proceso de investigación.

22. Shine KI. Some imperatives for clinical research. JAMA. 1997;278:245-246.
23. Murray CJL, Lopez AD, eds. The Global Burden of Disease. Cambridge, Mass: Harvard University Press; 1996.
24. National Advisory Mental Health Council. Genetics and Mental Disorders. Bethesda, Md: NIH Publication; 1998:98-4268.
25. National Advisory Mental Health Council. Priorities for Prevention Research at NIMH. Bethesda, Md: NIH Publication; 1998:98-4321.
26. National Advisory Mental Health Council. Bridging Science and Service. Bethesda, Md: NIH Publication; 1999:99-4353.
27. Astin JA. Why patients use alternative medicine: results of a national study. JAMA. 1998;279:1548-1553.

Une approche de Santé publique des thérapeutiques cliniques en psychiatrie : nouvelles voies de recherche

Le cadre conceptuel de la recherche thérapeutique dans le domaine de la santé mentale est en train de connaître une profonde mutation la faisant évoluer du modèle réglementaire étroit concerné uniquement par l’enregistrement et l’autorisation de mise sur le marché du médicament vers un modèle de Santé publique plus global. Ainsi, les études réglementaires classiques portant sur les médicaments traitant la démence excluent les patients présentant des symptômes psychiatriques et neurologiques ou les toxicomanes, et exigent qu’ils soient en bonne santé physique et qu’ils vivent avec un soignant. Ceci a pour conséquence d’élimer 90 % de la population présentant une maladie d’Alzheimer. Au contraire, le nouveau modèle de Santé publique vise à améliorer la prise en charge des patients en donnant la priorité aux préoccupations spécifiques des cliniciens, qu’ils s’agisse des aspects pratiques ou de ceux concernant les résultats : Est-ce que le traitement facilite le bon fonctionnement des patients ? Comment maintenir les patients dans un état de bonne santé mentale après avoir réussi à les équilibrer ? Pourquoi les traitements ne sont-ils pas aussi efficaces en pratique que lors des études cliniques ? Les études de Santé publique sont menées dans les conditions réelles de pratique avec des cliniciens pressés par le temps, prenant en charge un grand nombre de patients avec des tableaux cliniques incertains, des comorbilidades complexes, et des degrés variables d’interférences entre les variables d’observance idéaux. Ainsi, le centre d’intérêt autrefois dirigé exclusivement sur les symptômes s’est élargi pour intégrer les notions de fonctionnement du patient, de handicap, de morbidité, de mortalité, d’utilisation des ressources et de qualité de vie. Si la démonstration de la valeur du traitement passe toujours par les essais de recherche d’efficacité hautement contrôlés, ces derniers ne représentent désormais que l’étape initiale du processus d’investigation.

28. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. N Engl J Med. 1993;384:246-252.
29. Emmanuel NP, Cosby C, Crawford M, et al. Prevalence of herbal product use by subjects evaluated for pharmacological clinical trials. Poster presentation, 38th Annual New Clinical Drug Evaluation Unit (NCDEU) meeting, Boca Raton, Fl à;1998.
30. Lehman AF, Steinwachs DM. Patterns of usual care for schizophrenia: initial results from the Schizophrenia Patient Outcomes Research Team (PORT) Client Survey. Schizophr Bull. 1998;24:11-20.