The Research-to-Practice Gap in Mood Disorders: A Role for the U.S. Department of Veterans Affairs

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There is a persistent gap between the publication of research results and the translation of these findings to routine practice. It typically takes years to decades for a treatment proven efficacious in a randomized controlled trial to be adopted in routine care.[1,2] Further, for some treatments the risk-benefit profile may change substantially once disseminated.[3,4] This research-to-practice gap exists in part because most treatment studies are conducted in tightly controlled settings rather than real-world patient populations. Because these treatments are initially tested in selective settings with relatively healthy patients, such evaluations often do not consider efficacy or adverse effects in more vulnerable or complex populations cared for in real-world clinical care settings. The Institute of Medicine has called this the "efficacy-effectiveness gap,"[1] a phenomenon that characterizes dissemination of all medical interventions, including interventions for mental illness.[5,6]

The research-to-practice gap is especially concerning in mood disorders research. The lifetime prevalence of major depressive disorder exceeds 16% in the United States,[7,8] and up to 6% of the U.S. population is estimated to have bipolar spectrum disorders.[9] Mood disorders are among the most disabling conditions according to the World Health Organization Global Burden of Disease Study[10] and entail substantial personal and societal costs.[7,8] Notably, the high rates of functional impairment in bipolar disorder documented in the pre-pharmacologic treatment era have not lessened despite the introduction of modern treatments.[11]

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Moreover, the U.S. population is aging, and currently over 125 million individuals have at least 1 chronic medical condition, and 25 million have 3 or more chronic conditions.[12] Community- and primary care practice–based studies indicate that over half of patients with major depression have comorbid medical illnesses.[13,14] Among those with bipolar disorder, psychiatric and medical comorbidity is the rule rather than the exception.[15–19] Not surprisingly, mood disorder efficacy studies exclude many patients represented in clinical populations,[20] while mood disorder treatments may have less impact when applied to less selected populations.[21,22] Further, additional health risks associated with treatments may also become apparent when the treatments are used in heterogeneous populations.[23,24]

To optimally address the health of real-world patients with mood disorders, research efforts will have to move from efficacy-type studies to effectiveness studies, which include more complex patients treated under realistic clinical conditions, and then to dissemination and eventual sustainability in routine care.[25,26] That is, internal validity concerns (protocol structure) will have to be complemented by external validity (i.e., generalizability) considerations.[6] These issues have been raised periodically by mood disorders researchers over the past decade,[5,6,27–29] but have yet to be fully incorporated into our scientific thinking. Some public health–oriented researchers have now gone so far as to suggest that intervention studies should skip the efficacy stage and begin directly with trials in less selective, real-world samples.[30] While this suggestion seems radical, it is credible that moving more quickly to effectiveness-oriented research could not only reduce the time to public health impact, but also provide a more accurate assessment of intervention impact as is now emerging, for example, for the treatment of schizophrenia.[3,4]

Several aspects of the U.S. Department of Veterans Affairs (VA), including both the system itself and the population it treats, make the VA quite attractive for mood disorders research once one moves beyond the efficacy-predominant mindset and considers the entire spectrum of studies necessary to impact public health. The system itself functions as the world's largest staff model health

maintenance organization (HMO), and as such provides integrated clinical services for a wide range of disorders with a standardized benefit package. Unlike most health care systems, for which mean health plan enrollment time is measured in months, veterans tend to continue to receive services over longer periods of time. There exists an extensive registry of the entire population of system users, which provides an accurate denominator as well as demographic characterization and case-finding for clinical studies. The powerful electronic medical record data system allows researchers to collect comprehensive data in a cost-efficient manner, without having to rely on intensive primary data collection or link several data sources from different provider organizations or health plans.

In addition, the VA serves a population disproportionately affected by mental disorders, since the modal age of military service is also the peak age at onset for a variety of common yet serious mental disorders. For example, the VA serves almost 80,000 individuals with bipolar disorder each year.[31] Although still serving a predominantly male population, the VA also serves increasing numbers of women and minority individuals across multiple generations ("Baby Boomers," "Generations X and Y"), with the proportion of women veterans now exceeding 6% (1.6 million).[32,33] These features of the VA health care system make it an appealing setting for 3 important types of studies: clinical and health services observational studies, clinical trials, and dissemination studies.

Among health services observational studies, several key pharmacoepidemiology studies have already been conducted using VA data, including the early studies demonstrating increased risk of diabetes among patients taking atypical antipsychotics.[23,24] Clinical studies are enhanced by the availability of national datasets and site-level electronic medical record data to facilitate identification and follow-up of potential subjects. Further, such well-characterized but unselected populations provide a different view of utilization, co-occurring conditions, course, and outcome than that derived from tertiary care–based studies. Similarly, such unselected populations may be particularly informative in genetic studies, where endophenotypes may not correspond to the DSM-defined diagnoses that often serve as entry to specialty clinics.[34,35]

The VA has a long history of involvement in clinical trials for mood disorders, including conducting the first lithium studies in bipolar disorder in the United States, which led to lithium's approval by the U.S. Food and Drug Administration.[36–38] More recently, VA sites were well represented in a large trial of care management for late-life depression in primary care.[39] Care management trials have now been extended to bipolar disorder, and results in a highly comorbid VA sample[40,41] resemble those in a private health plan population.[42] As noted above, nationwide and facility-specific electronic datasets allow the establishment of registries and patient tracking mechanisms valuable for subject identification and follow-up for clinical trials. Moreover, the VA has established national centers of expertise in clinical trials (VA Cooperative Studies Program: http://www1.va.gov/resdev/programs/blrd-csrd/csp.cfm) and health economics (Health Economics Research Center: http://www.herc.research.va.gov/home/default.asp).

The VA is also at the forefront of the emerging field of implementation/dissemination science. This field utilizes a variety of strategies to identify optimal methods to disseminate effective interventions across routine care settings, addressing individual, provider and system factors in coordinated fashion.[43] Currently, the VA is spearheading initiatives to implement evidence-based depression care management programs in primary care settings[44] and recovery-oriented treatment models in mental health specialty settings.[45] An important component of the VA health care research budget is targeted exclusively to implementation science via the Quality Enhancement Research Initiative programs (http://www.hsrd.research.va.gov/QUERI/).

The early promise of collaboration between the VA and the National Institute of Mental Health (NIMH) in mood disorders research[36–38] has yet to be fully realized, though other National Institutes of Health institutes have an established record of joint research with the VA,[46–48] as does the Agency for Healthcare Research and Quality (see, for example, http://grants.nih.gov/grants/guide/pa-files/pa-02-066.html).

Nonetheless, the VA's unique informational and clinical infrastructure supports the efficient conduct of pharmacoepidemiology studies, large effectiveness-oriented trials, and dissemination studies to benefit the complex real-world patient population with mood disorders. Further, the VA's research funding stream complements that of the NIMH and includes opportunities for career development awards as well as investigator-initiated projects in these areas. Thus, as one moves beyond an efficacy-dominant mindset to consider the full range of studies necessary to impact public health, the VA's value as a site for mood disorders science becomes readily apparent.

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