Keller Autobiography

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I am greatly honored that the CINP has asked me to write an autobiographic chapter for this volume. I am also humbled by the magnificent achievements of other scientists in the field and rec- ognize that most of what I have done involves collaboration with others. My profound thanks go to all who have inspired, taught, and worked with me directly, and to those patients who have shared so much of themselves as research subjects.

During my first year of residency at Harvard and the Massa- chusetts General Hospital (MGH) in 1974, I asked Ross Baldes- sarini how long I should keep a patient on medication after an ep- isode of depression. His reply: "No one knows; you need to rely on your own clinical judgment." My response: "Why does no one know?" His: "Because there are no treatment studies of depression lasting longer than 6 to 8 weeks."

That encounter was a defining moment for me. After the sem- inar with Ross, I researched the literature and found that, besides the absence of long-term treatment studies for depression, there were no studies that prospectively assessed the course of mood disorders over time with structured clinical interviews and criteria-based diagnoses. This led to my decision to pursue a career focusing on long-term prospective, naturalistic studies of depression, other mood disorders, and anxiety disorders in adults, adolescents, and children, as well as studies involving acute and long-term maintenance treatment for these conditions with pharmacotherapy, psychotherapy or a combination of the two.

My first research project was assisting in a study involving 955 patients from five medical centers who were seeking treatment for depression. (The academic centers involved then were MGH, Harvard Medical School, Boston; New York-Presbyterian Hospital, Columbia Univer- sity, New York City; Washington University School of Medicine, St. Louis; University of Iowa College of Medicine, Iowa City; and Rush-Presbyterian -St. Luke's Medical Center, Chi- cago) The study initially included only one follow-up interview with participants. I was con- vinced that if we re-interviewed the same people at short intervals over many years, we would learn the answers to some of the important questions about lifetime course and outcome of mood disorders.

So here I was, a lowly resident, repeatedly asking the study's principal investigators (Ger- ald Klerman, Jean Endicott, Bob Spitzer, Nancy Andreasen, Paula Clayton, George Winokur, Jan Fawcett, Bill Coryell, Robert Hirschfeld, and Bob Shapiro) to include an ongoing fol- low-up component to their research project. I couldn't let go of the fact that this would be an extraordinary opportunity. The follow-up component was added and, in 1977, I was asked to head the study's MGH site when the PI at the site, and chair of the project's steering commit- tee, Gerry Klerman, left MGH to become became head of the national agency for Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA).

Since that time, I have been the principal investigator for the MGH site (now located i n Providence, RI, at Brown Medical School) of the "NIMH Collaborative Depression Study" (CDS), which is now in its 26th year. Initially, I hoped to follow subjects for at least 5 years but never dreamed that it would be 25 years -and still going! Since 1992 I have also been chair of the study's steering committee. Original enrollment was 955 patients with a

mood disorder (who served as the probands), more than 3,000 first-degree relatives, approximately 500 spouses and significant others,and more than 200 controls. The relatives were followed-up af- ter 6 years, and the probands have since been followed at either 6-month or 1-year intervals. We are fortunate that the investigation has been funded since its inception by NIMH grant awards.

To date, the CDS research team has produced more than 240 publications and our findings on clinical course plus those of Jules Angst of Switzerland, who also conducted a follow-up study of approximately 200 subjects with mood disorders at 5-year intervals (1,2), have had a major role in shaping how the field understands the long-term course of mood disorders. Largely because of data published by Angst and by the CDS, it has been established that affec- tive disorders are primarily chronic illnesses with powerful tendencies for relapse and recur- rence that most often are lifelong in nature and have meaningful residual subsyndromal symp- toms and widespread psychosocial impairment in the intervals between episodes (3). As we have learned from other fields of medicine, when dealing with a chronic ilfuess, there i s no substitute for prospecti ve longitudinal study of the course of that illness. Perhaps the best ex- ample of this is the National Institutes of Health 's Framingham Heart Study of cardiovascular disease. Its prospective and longitudinal design has yielded important information about risk factors, patterns oflongitudinal course, and sequelae of heart disease that could not have been derived by any other type of research design. The CDS is a unique example of just such a study in psychiatry.

Two years after receiving a diagnosis of depression, 20% of our CDS patients still had not recovered from their initial episode of depression, and 75% suffered a relapse/recurrence within 10 years (4). By 20 years, 5% still had not recovered from their initially diagnosed con- ditions, and 92% who had recovered had at least one relapse/recurrence (Keller MB, unpub- lished data). In 1982, a colleague, Robert Shapiro, and I had identified a condition since called "double depression," characterized by an episode of major depression that is preceded by at least two years of chronic mild depression (5). For the 25% of depressed patients with double depression, dysthymia typically remains even after the episode of major depression ends. This is why treatment often needs to continue beyond an acute phase of the illness.

Due to the chronic nature of mood disorders, there is a need for reliable instruments for measuring course over long periods if we are to learn more about their natural history. Early on in my career, Robert Shapiro and I developed the Longitudinal Interval Follow-up Evalua tion (LIFE), the first structured comprehensive follow-up assessment instrument to measure a patient 's psychopathology and treatment on a weekly basis (6). To date, the LIFE has been used in more than 1,000 clinical and treatment outcome research projects internationally , and the assessment materials have been translated into more than 12 languages. There are also ver- sions of the LIFE for use with children, adolescents, and elderly patients.

The LIFE provides an alternative to other measures used to assess psychosocial function- ing (6). A clinical interviewer (in-person or by phone) uses the LIFE to collect detai led psychosocial, psychopathologic, and treatment information for each subject. When used in conjunction with an intensive training and rater monitoring system, it is a reliable instrument for longitudinal studies. Interviewers score taped interviews to ensure long-term inter-rater re- liability. The psychiatric status ratings (PSR) provide a separate, concurrent record of the course of each disorder initially diagnosed or that develops during follow-up. Any DSM-IV disorder can be rated with the LIFE, and any length or number of follow-up intervals can be accommodated. For the first five years of the CDS study, subjects were interviewed every six months; after that, interviews have been done every year.

Patients with depression describe feeling sad or unhappy, not having energy, or being irrita- ble. They feel m;erable and are unable to enjoy life. Usually they'll say that the symptoms have been getting worse over the past couple of weeks or months. About 25% of patients will admit to feeling "down" for at least 2 years before their current acute bout of depression (7). Ironically, patients with double depression often improve spontaneously or respond rapidly to treatment – or they think they do. They often improve to the point where they're feeling the way they did before the acute major depression set in, i.e., they have returned to their usual state of chronic low-level depression (dysthymia). However, they then believe they are better, because they've come to see that state as part of their personality or character. It is still a low-grade chronic depression that we have recently come to learn is amenable to treatment, as is the major depression, meaning that with treatment past this phase, fratients usually end up feeling better than they can remember.

In 1982, I took the lead with other members of the CDS team, including Phil Lavori, a stat- istician, and found that the vast majority of patients seeking treatment as inpatients (80% of CDS sample) and those seeking treatment as outpatients (20% of sample) had not received pharmacotherapy for depression or had received pre-study subtherapeutic doses far too briefly, despite having a major depression for at least 6 months (7). Only 3% of patients re- ceived a dosage of 2:250 mg/day, and only 18% received a dosage of 150 mg/day, of imipramine or its equivalent. Later, my CDS colleagues and I reported that only about half of our hospitalized subjects and approximately one-third of those treated as outpatients received a therapeutic dose of medication for their depression after the first 8 weeks of "treatment" (8). I was stunned and dismayed by these data and vowed to focus on ways to solve the probl em of under-treatment of patients. Our finding had a major impact on the fields of psychiatry, gen- eral medicine, and public health because it demonstrated the enormous gap between available treatments for depression and actual usage.

By the early 1980s I became convinced that what we were learning about the clinical course of mood disorders would have great value if the data could help to inform the design and implementation of treatment research on these severe mental illnesses. This beliefled to my first participation in a neuropharmacologic treatment study: a double-blind, randomized clinical trial to test the hypothesis that the current standard dose oflithium (0.8-1.0 meqL) was more advantageous in preventing relapse than,lower doses (0.4-0.6 meqL) (9). We considered this highly important because of the concern that higher doses may lead to either thyroid or re- nal disease over the long-term, and we wanted to determine the lowest effective dose. My col- leagues included John Kane, Alan Gelenberg, Phil Lavori, and Jerold Rosenbaum, each of whom taught me much about how to design and conduct a double-blind, randomized clinical trial. We were fortunate to have a positive finding that the standard dose of lithium resulted in an almost four times less likelihood ofrelapse and recurrence that the lower dose. (Since then we have also learned, from the research of others, that the fears of thyroid or renal damage af- ter standard dose treatment were unfounded.)

The lithium study (a double-blind, randomized , placebo-controlled , maintenance design) marked a profound turning point in my career because from that time forward I've been hooked on the excitement oflong-term treatment studies. My passion for prospective , natural- istic long-term clinical research of mood and anxiety disorders would be complemented by the design of treatment studies of mood disorders in children, adolescents, and adults with pharmacotherapy or structured psychotherapies.

Because chronic forms of major depression, including double depression, are associated with a high rate of prevalence, impaired functioning, and suicidality, I directed a study involv- ing a consortium of 12 medical centers which was the first to determine

the efficacy of long-term treatment for these illnesses. Our findings, published in 1998 (10), represented the initial report of a randomized controlled trial of treatment for chronic major depression and double depression and for maintenance therapy to prevent recurrence. During an 18-month period, we studied 161 outpatients with chronic major or double depression who responded to sertraline in a 12-week trial and who continued to have a satisfactory therapeutic response during a subsequent 4-month continuation phase.During the double-bGnd, randomized main- tenance phase, patients who received placebo were four times more likely to suffer a recur- rence of depression than patients who stayed on active medication. It was unanticipated that such a high proportion (greater than 50%) of patients who were chronically depressed for more than 20 years would initially respond to 12 weeks of medication and continue to improve on the same medication in the continuation phase.

I was extremely pleased with the results of the maintenance study describd above but still wanted to verify the long-held, but not yet tested, belief that treating chronic depression with medication and a structured psychotherapy was more beneficial than treatment with medica- tion alone. The multicenter study that I designed and directed (involving the same sites and in- vestigators as the previous study) compared the use of nefazodone, the cognitive behav- ioral-analysis system of psychotherapy (CBASP), and their combination in the treatment of chronic depression. Among patients who completed 12 weeks of treatment, those who re- ceived the combined medication and CBASP had a highly statistically significant and clini- cally meaningful greater response rate (85%) than either the patients who received medication only (55%) or CBASP alone (52%) (11). This was the first large-scale study of psychotherapy combined with medication in patients with chronic forms of major depression, and the magni- tude of the comparative benefit of combined therapy was a pleasant surprise that suggested its use should be considered more often in the routine treatment of patients with this diagnosis.

Depression is a mental illness with an unknown etiology. Theories starting in the 1960s (and evolving considerably in the following three decades) focused on a deficiency of seroto- nin or norepinephrine in the synapses of the brain. It is currently believed that our knowledge about brain receptor neurobiology represents only an end stage in a more complex sequence of abnormalities that involve intraneuronal secondary messengers triggered by as-yet-unknown neurobiological changes and, ultimately, gene sequence abnormalities. Most researchers be-lieve there is a genetic component as a result of familial aggregation studies, studies of monozygotic twins reared apart, the fact that the illness affects twice as many women as men, more advanced measurements of brain physiology, and the mapping of the human genome.

When I was an undergraduate at Dartmouth College in the late 1960s, the first generation tricyclic and monoamine oxidase inhibitor antidepressants were first coming into widespread use, and little was known about how they worked or how effective they were over time. I de- cided to go to medical school, rather than become a psychologist , because by becoming a psy- chiatrist I could not only do research and practice psychotherapy but could prescribe medica- tion when needed and understand the full range of medical illnesses and their relationship to mental illness. Psychiatry was not a popular medical specialty for a career -not only was there a stigma against patients with mental illness but also against those who wanted to work with them. If you expressed an interest in psychiatry, people thought there was something wrong with you, or that you chose the specialty because you could not become a cardiologist or a sur- geon – a "real doctor."

As a medical student at Cornell in New York, I was inspired to pursue psychiatry by Paul McHugh who strongly advocated understanding the phenomenology of mental illness, estab- lishing common criteria for diagnosis, and discovering the neurobiological bases of the major mental illnesses. Paul went on to have a most distinguished leadership career in

psychiatry, and served as chair of the department of psychiatry at Johns Hopkins Medical School for more than 25 years.

During my residency at MGH, two senior professors and mentors played a major role in shaping my career. Gerry Klerman is one of the founders of modern psychopharrnacology, a brilliant innovator, and acreative researcher, educator, and therapist. Gen-y Klerman later be-came head of ADAMHA and then director ofresearch in the department of psychiatry at Cor- nell Medical School. Aaron Lazare taught me how to elicit the needs and "complaints" of pa- tients, which often went unstated, and served as a model for the importance of a true biopsychosocial understanding of mental illness. He was an astute clinician who readily trans- lated clinical observations into research ideas and scholarly writings. Aaron Lazare went on to serve as chair of the department of psychiatry at the University of Massachusetts Medical School, where he is currently chancellor and dean .

After completing medical school in New York and my residency at MGH in Boston, I be-came director of ambulatory services and director of clinical research in psychiatry at MGH. In 1989 I became chair of the department of psychiatry and human behavior at Brown Univer- sity's School of Medicine in Providence, Rhode Island. I still hold this position and am also the executive psychiatrist -in-chief at the seven Brown University-affiliated hospitals.

In addition to the CDS, I currently have two separate long-term prospective naturalistic studies underway involving adults with anxiety disorders. The first is the Harvard/Brown Anxiety Research Program (HARP), which involves more than 700 adults seeking treatment in a psychiatric setting who have been followed prospectively for a minimum of 12 years. The second study is a complementary study of 540 adults who presented to a general medical set- ting for a non-psychiatric medical illness and were found to have an anxiety disorder by our research team. This cohort of subjects has been followed annually for a minimum of five years.

I am also the Pl for a study including approximately 400 children and adolescents with bi-polar disorder. My collaborators on this project are Henrietta Leonard, Tony Spirito, and Syl-via Valeri (Brown University); Boris Birmaher, and Neal Ryan (Western Psychiatric Institute in Pittsburgh); and Michael Strober (UCLA). Finally, I direct several multi-institutional ran-domized clinical trials to study the safety and efficacy of antidepressants and psychotherap y (alone or in combination) in adults and adolescents with bipolar and unipolar illness; several multi-site studies of the acute, continuation, and maintenance treatments of chronic major de- pression and double depression; and a separate long-term study ofrecurrent depression.

As much as I remain excited about directing my own research programs, I receive enor-mous gratification in helping train the next generation of mental health researchers, at Brown and at other medical centers where I mentor young psychologists and psychiatrists. Further- more, I feel strongly about the need to provide adequate treatment for those suffering with de- pression and to educate not only psychiatrists but also family and primary-care physicians about how this might be accomplished.

Depression is a debilitating illness for an individual and a major public health problem . A study dohe in 2001-2002, and published in June 2003 by the National Comorbidity Survey Replication group, found that the lifetime prevalence of depression in the United States is 16.2%; approximately 1 in 6 or 35 million Americans will experience the illness in their life- time (12). Ronald Kessler's group also found that each year 13 to 14 million (approximately 6.6% of Americans) experience moderate to severe depression. Other studies estimate depres- sion costs of $53 billion a year in workers' lost productivity (13,14). Although these studies were limited to the US, several other reports have found

similar lifetime rates of 16% and an- nual rates of 4-6% of the population) (15). The World Health Organization 's Global Burden ofDisease Study Project found that major depression is currently the leading cause of disability in the developed countries of the world (16). In addition, depression often occurs early in life: 25% of those who have depression had their first episode before age 18 and 50% before age 22.

The National Comorbidity Survey discovered that approximately 57% of Americans with depression lasting at least 12 months sought treatment (13) (an increase from 30% ten years ago), but fewer than 25% received at least minimally adequate treatment. As we reported in 1982, using data from the CDS, not enough people who suffer from depression were getting the right treatment in the right dose for a long enough period of time. The lack Qf appropriate treatment still exists, despite greater awareness of depression and less stigma attkhed to those who have it; this is due partly to the celebrities and other public figures who have openly dis- cussed their experiences with the illness. Because many individuals with symptoms of depres- sion tum to a primary-care or family physician for help, it is necessary that these health-care providers become highly skilled at recognizing depression and other mood disorders and are knowledgeable about evidence-based treatment guidelines for both drug therapy and psycho- therapy. This is particularly important because depression is often comorbid with other psy- chiatric conditions, such as anxiety disorders, alcoholism and drug dependence, and with non-psychiatric medical conditions, including cardiovascular disease.

For those reasons, I have become especially interested in encouraging psychiatrists to work with primary-care physicians to improve their understanding of treatment outcomes for de- pression and, ultimately, to increase remission rates and patient compliance with treatment. To reach a.general medical audience, I recently published an article in the Journal of the Ameri- can Medical Association' s special issue on depression (17), describing the need for specific criteria to determine effective treatment outcomes. At a time when treatment decisions and re- imbursement of costs need to be increasingly evidence-based, we must be clear about defining optimal treatment outcomes in depression. For many chronic medical illnesses (e.g., hyper- tension, diabetes, or hypercholesterolemia), a physician treats a patient until specific criteria. (outcomes criteria) have been met that indicate a return to a healthy state. Treatment continues until that time and the patient continues with maintenance treatment to prevent a return of the condition. When treating depression, the outcomes goals are not as clearly defined and not based on the results of specific laboratory tests or procedures. In the 1990s, clinical evidence showed that achieving remission is associated with better long-term outcomes when eom- pared with achieving response without remission (18). Patients who had attained remission status had significantly greater improvement in psychosocial functioning (e.g., quality of life, work functioning, interpersonal functioning, and physical health) than patients who had achieved only a therapeutic response. Therefore, remission (i.e., a state of minimal or no symptoms and a return to normal functioning) is considered the optimal outcome of treatment, although there is no single standardized definition or set of criteria for the term

Only in the last decade have attempts been made to establish standardized definitions and operational criteria for determining treatment outcomes. Remission criteria should continue to be based primarily on reduction in the number and severity of symptoms using specific end- points of rating scales, such as a total score of 7 or less on the Hamilton Rating Scale of De- pression (HAM-D), or a total score of 10 or less on the Montgomery-Asberg Depression Rat- ing Scale (MAcyS) (18). These scores have been shown to reliably differentiate those who do not have depresion from those with even mild depression, who can benefit from treatment. A patient's status would be furthered classified on the basis of 1) the absence both of symptoms and functional impairment

for at least four weeks (the optimal outcome); 2) no symptoms but with minimal impairment in psychosocial functioning; and 3) both symptoms and impairment in functioning to a mild degree.

Neurobiological research on depression has shifted from a focus on the interaction between neurotransmitters and cell surface receptors to one on gene expression and structural and functional changes within the brain. Therefore, future remission criteria are likely to include measures of improvement developed from neuroimaging studies and from neuropatho- physiologic and genetic research. I am hopeful that this new knowledge will enable us to know when patients are in a true state of recovery and will remain well without continued treatment.

Few of the classifications, scales, and scores for determining treatment outcome are now used by psychiatric or primary-care practitioners to identify their patients with depression. Psychiatrists need to use the variety of available psychosocial and pharmacologic treatments and to appreciate the importance of long-term treatment even after symptoms have disap- peared -it's not just about being better; it's about being well. It is very rewarding to be part of an effort to increase the number and ability of clinicians who can attain that goal for patients suffering the often debilitating effects of depression. As I look back nearly 30 years to the be- ginning of my residency, I am in awe of the incredible amount of knowledge gained about the underlying basis of mood disorders and how best to treat them.