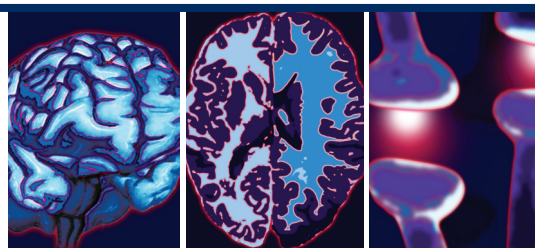
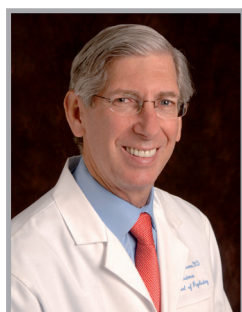


INTERVIEW



In search of the pathophysiology and prevention of schizophrenia



Jeffrey A Lieberman[†]: Jeffrey A Lieberman is currently the Lawrence E Kolb Professor and Chairman of Psychiatry at the Columbia University College of Physicians and Surgeons and Director of the New York State Psychiatric Institute. He also holds the Lieber Chair and Directs the Lieber Center for Schizophrenia Research in the Department of Psychiatry at Columbia. Dr Lieberman received his medical degree from the George Washington School of Medicine in 1975. Following his postgraduate training in psychiatry at St. Vincent's Hospital and Medical Center of New York Medical College, he was on the faculties of the Albert Einstein College of Medicine

and Mount Sinai School of Medicine. Prior to moving to Columbia University he was Vice Chairman for Research and Scientific Affairs in the Department of Psychiatry and Director of the Mental Health and Neuroscience Center at the University of North Carolina at Chapel Hill School of Medicine. Dr Lieberman's research has been supported by grants from the NIH and the NARSAD, Stanley, and Mental Illness Foundations and has focused on the neurobiology, pharmacology and treatment of schizophrenia and related psychotic disorders. In this context, his work has advanced our understanding of the natural history and pathophysiology of schizophrenia and the pharmacology and clinical effectiveness of antipsychotic drugs. In terms of the latter, he served as Principal Investigator of the Clinical Antipsychotic Trials of Intervention Effectiveness Research Program (CATIE), sponsored by the National Institute of Mental Health (NIMH). He also currently serves as Principal Investigator on the NIMH contract Recovery After an Initial Schizophrenia Episode (RAISE) and will lead a multi-institution research team in developing and testing an evidence-based strategic intervention for early psychosis to demonstrate how treatment at the onset of symptoms can prevent the debilitating effects of schizophrenia and related psychotic disorders. In collaboration with The University of North Carolina, Dr Lieberman leads the Clozapine-Induced Agranulocytosis Consortium (CIAC) project at Columbia University as a newly awarded NIMH addition to the Genome-Wide Association Study to Detect Genetic Variation for Schizophrenia aiming to detect genetic markers that predict side-effect vulnerability, including that for agranulocytosis caused by antipsychotic drugs. His work has been reported in more than 500 articles in the scientific literature and he has edited or co-edited eight books, including the textbook *Psychiatry*, currently in its third edition; *Textbook of Schizophrenia*, *Comprehensive Care of Schizophrenia*; *Psychiatric Drugs*; and *Ethics in Psychiatric Research: A Resource Manual on Human Subjects Protection*. He also serves, or has served, as Associate Editor for the *American Journal of Psychiatry*, *Biological*

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Psychiatry, Neuropsychopharmacology, Acta Psychiatrica Scandinavica, Schizophrenia Research, Neuroimage, International Journal of Neuropsychopharmacology and the *Schizophrenia Bulletin*. Dr Lieberman is a member of the National Academy of Sciences Institute of Medicine and recipient of the Lieber Prize for Schizophrenia Research from NARSAD, the Adolph Meyer Award from the American Psychiatric Association, the Stanley R Dean Award for Schizophrenia Research from the American College of Psychiatry, the APA Research Award, the APA Kempf Award for Research in Psychobiology, the APA Gralnick Award for Schizophrenia Research, the Ziskind-Somerfeld Award of the Society of Biological Psychiatry, the Ernest Strecker Award of the University of Pennsylvania, the Exemplary Psychiatrist Award from the National Alliance of the Mentally Ill, and the Lilly Neuroscience Award from the Collegium Internationale NeuroPsychopharmacologicum (C.I.N.P.) for Clinical Research. Dr Lieberman is a Fellow of the American Association for the Advancement of Science (AAAS), the American College of Neuropsychopharmacology (ACNP) and the American Psychopathological Association, a Distinguished Fellow of the American Psychiatric Association (APA), and a member of the Dana Alliance for Brain Initiatives (DABI). He is, or has been, a member of the advisory committee for Neuropharmacologic and Psychopharmacologic Drugs of the US FDA, the Planning Board for the Surgeon General's Report on Mental Health, the Committee on Research on Psychiatric Treatments of the APA, the APA Work Group for the Development of Schizophrenia Treatment Guidelines, the Brain Disorders and Clinical Neuroscience Review Committee, and the National Advisory Mental Health Council of the National Institute of Mental Health. He currently chairs the APA Council of Research, is a member of the board of directors of the American Psychiatric Foundation of the APA, is on the Medical Advisory Board of Fountain House in New York City, is vice-president of the C.I.N.P., and is co-chairperson of the Ethics Committee of the American College of Neuropsychopharmacology (ACNP). Dr Lieberman lives with his wife and two sons in New York City.

Q When did you develop an interest in schizophrenia and related disorders and what instigated this interest?

I became interested in schizophrenia as a medical student and as a resident training in psychiatry. What attracted me to schizophrenia and mental illness, in general, was a fascination with the brain; trying to understand how the brain was the organ that orchestrated the past repertoire of behavior, emotions and intellectual thoughts – the essence of what made people individuals. In terms of studying diseases of the brain and disorders of the mind, it was clear to me that, among the major psychiatric illnesses, schizophrenia really stood out and might even be considered as the prototype. It was an illness that people thought of when they thought about people being ‘crazy’, ‘round the bend’ or ‘disturbed’. It reflected one of the grossest destructions of a person's mental functioning in terms of psychosis and losing touch with reality and also, tragically, it tended to affect people early in life when they were coming into their prime. There was a particular poignancy and tragedy associated with schizophrenia that involved children growing up, maturing during adolescence – about to enter into the prime years of their life – and then all of a sudden becoming afflicted with this

disturbance in their mental functioning, usually not knowing what this was due to, where it came from or how to deal with it, and unfortunately for the vast majority of people, they were never the same again, or even if they did recover, they went on to have subsequent episodes and ultimately became disabled. So it seemed that if one was interested in the brain and behavior, the study and treatment of schizophrenia was really one of the most important, if not the most important, places to start.

Q Which researchers have most influenced or inspired your research?

There are a large number of individuals who inspired my career and who I respected, and tried to model my own work on over the years. These were senior figures in the field who, when I was growing up and training, I admired and they shaped my world. So I would point to people like Eric Kandel (Columbia University, USA), Solomon Snyder (Johns Hopkins University, USA), Don Klein (Columbia University), Robin Murray (Kings College, UK), Tim Crow (Oxford University, UK), Eve Johnstone (Edinburgh University, UK), Bob Spitzer (Columbia University), Richard Wyatt (National Institute of Mental Health [NIMH]),

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USA), Will Carpenter (University of Maryland School of Medicine, USA), John Kane (The Zucker Hillside Hospital, USA) and more contemporary influences, such as Dan Weinberger (NIMH), Ken Kendler (Virginia Commonwealth University, USA), and Ken Davis (Mount Sinai Medical Center, USA).

Q What do you feel are the most important contributions you have made to schizophrenia research?

I regard myself as a clinical researcher who has tried to understand the advances in technology and methodology in biomedical research and how best to apply them to understanding human mental disease, particularly schizophrenia. In the course of doing so, I think my major contributions can be described as having served to improve the prognosis of people who have schizophrenia. When I was in training, in the 1970s, the notion of schizophrenia conjured up doom and gloom – there was a certain therapeutic nihilism associated with the illness and it was thought that in people with schizophrenia the way their brain developed was somehow genetically abnormal. Once the onset of illness occurred we might be able to suppress the psychosis but we could not prevent the progression of schizophrenia and the clinical deterioration associated with its ultimate disability of the individual. There was a certain sense of inevitability of the morbidity of the illness and that made clinicians far less optimistic, far less aggressive in their treatment and far less encouraging in trying to foster recovery than was really warranted. Much of my work has been in the therapeutics of schizophrenia, specifically, developing better treatments and trying to minimize side effects associated with treatments that lead people to not be adherent with medication. I would like to think that I, along with other investigators, were some of the first to dispel the notion of inevitable deterioration and disability with schizophrenia and that was done by a series of studies that focused on patients in the early stages of the illness. Essentially, in the late 1980s and early 1990s, a series of studies were conducted that examined the course and outcome of patients in their first episode of schizophrenia. The findings of these studies were quite positive in terms of the level of treatment response and rates of remission and recovery. This led to a new understanding of the illness, as a progressive illness that

may have its origins in certain risk genes and may begin in adolescence or young adulthood, first expressing itself through a prodromal phase before crystallizing into the symptoms by which the illness is diagnosed. However, intervention in that period can achieve successful remission and prevent recurrences. This strategy can, to a considerable degree if not completely, prevent progression from leading to persistent morbidity and disability.

These treatment and follow-up studies were augmented enormously with the advent of modern noninvasive neuroimaging methods: first CT scans and next MRI and PET scans. With these tools it could be demonstrated that patients, over time (particularly when you began examining them in the early phase of their illness), had a progressive loss of brain gray matter in specific anatomic regions. So this led to a hypothesis that the progression of the illness was associated with this loss of gray matter and that the target of treatment was to prevent this loss of gray matter and the consequent illness progression. This hypothesis led to a new way of thinking about the illness on a pathophysiological level as well as a therapeutic level and gave rise to what became known as the early detection early intervention movement. This movement had its origins in studies of first-episode or early-stage schizophrenia, which was then extended to the presyndromal phase of the illness or to what has been called the prodromal stage of the illness – that stage where people are beginning to experience the first expression of disturbances in their mental function but not severe enough or fully formed enough to meet syndromal criteria. The idea of trying to interdict the illness before it ever really gets started, by intervening during this prodromal period, I think, has captured the field's imagination, and you have programs for early detection/intervention in the prodromal phase that have sprung up all over the world – we even have a professional association that has developed – the International Early Psychosis Association. I would say my most important contribution was being part of the research effort that led to improving the prognosis of the illness by developing better therapeutics and producing an evidence base that demonstrated that if you can identify and treat patients earlier in the course of illness and minimize the duration of their untreated illness you could improve their prognosis and to a considerable degree and foster their recovery.

“I would say my most important contribution was being part of the research effort that led to improving the prognosis of the illness by developing better therapeutics...”

“Our field has become multi-disciplinary and the best science is being conducted by teams collaborating using these various approaches.”

Q Your research over the years has covered topics ranging from neurobiology to psychopharmacology. Which areas do you feel are currently the most progressive and exciting?

I would say that the most exciting scientific development in my professional lifetime, which has revolutionized the field, is the advent of modern human genetics. Progression from genetic profiling with restriction length polymorphisms, to identification of single nucleotide polymorphisms, development of genome-wide association (GWA) scans, to the understanding of copy number variants and inherited and *de novo* mutations, and then finally, entering the era where exome analysis and deep sequencing of genes can be done by the developing technology that will allow individual genomes to be sequenced affordably and quickly at a very high level of resolution. However, even though genetics has become a major strategy in biomedical research, including research on the brain and mental illness, it has yet to bear real clinical impact on mental illness, but I am confident that the time is not too far in the future.

Another area that has been transformative has been the advent of modern imaging techniques. It began with CT scans but it has really been the various applications of MRI, including structural MRI and functional MRI, and spectroscopic imaging that have provided enormous abilities to examine different aspects of the brain *in vivo*, longitudinally and noninvasively. In addition, PET scanning has allowed for neurochemical characterization of neurological function.

Recently, we have acquired the ability to apply basic science methodology to develop animal models and study new treatment mechanisms for mental illness. For example, the whole area of optogenetics is unbelievably exciting – being able to introduce changes in cells and then activate them through exposure to light. And then there is the whole area of induced pluripotent stem cells, which allows for genetically engineering cells and then applying them in a way that can be therapeutic.

Another area of great interest is the development of therapeutics. For most of the history of modern psychiatry, therapeutics has been largely dependent on serendipity, and then working backwards to determine how a drug works and determining what that means in terms of the pathophysiology of the illness. Now we have more rational and prospective strategies for drug development: having a drug target either that has been identified as

a gene product or some neurobiological substrate, developing a small molecule targeting the protein, validating it in animal assays and then transferring it to humans for proof-of-concept studies. So what you might call a theory-driven method of drug development, has really taken hold in the field and is a very positive development.

The challenge for clinical researchers like me is how we bring these tools to bear in the study of mental illness; and it was not too long ago that, for psychiatry, the gap was too wide and it was too difficult – the basic science could not be easily applied. However, that has all changed and it is now conducted in most major academic medical centers by increasing the number of investigators who are trained in these methods. Our field has become multi-disciplinary and the best science is being conducted by teams collaborating using these various approaches.

Q Much of your recent work has focused on genetics and pharmacogenetics in schizophrenia; are we close to achieving truly personalized therapy?

Genetics is something that has held promise for medical illnesses for several decades now, but the rewards have tantalizingly eluded us for the most part. I remember the first study, published in *Nature* by Hugh Gurling (in 1988) where he identified the specific gene locus on chromosome 5 that was supposed to be associated with schizophrenia [1]. We thought this was the beginning of the diagnostic test for schizophrenia and, ultimately, the discovery of the cause of schizophrenia. Lo and behold, this was never replicated and subsequently there were an endless series of genetic associations that could not be replicated or were not very robust. We now have, as a result of studies that have identified single nucleotide polymorphisms, risk alleles, as well as copy number variants and mutations, a robust convergence of findings on approximately a dozen different genetic loci that are associated with mental illnesses such as schizophrenia, bipolar disorder and autism – overlapping in some cases – which are providing a much better understanding of genetic risk architecture and mechanisms of heritability. Nonetheless, we still have not realized or arrived at the level where they are applicable, both in terms of diagnostic categorization, as well as in terms of guiding treatment. However, I am absolutely convinced that it is only a matter of time, and that we are on the right track. The methodologies are getting more powerful, but the question is,

how and when can these applications be clinically implemented and begin to introduce personalized medicine? Is this just around the corner or further down the road? If I was pressed to hazard a guess, I would say we are looking at a 5–10-year timeframe, but that is purely speculation.

Q In 2005, you published a seminal paper (in *New England Journal of Medicine*) detailing a large study on the efficacy of antipsychotic drugs in patients with chronic schizophrenia. Now, over 5 years later, how much better is our understanding of these drugs and their side effects?

I think our understanding of the drugs, in terms of their efficacy and side effects, is considerably better. We have scaled down our beliefs and expectations to a more realistic level and have a sense of what these medications are able to do, and what is their rank order comparatively in terms of efficacy and safety. I cannot say, however, that there has been much progress in the quality and novelty of the drugs. In 2005 we published results of the Clinical Antipsychotic Trials of Intervention Effectiveness Research Program (CATIE) study in the *New England Journal of Medicine*, which were highly unexpected – it was like an emperor’s new clothes type of finding – that the new drugs were not much better, if at all, than the older antipsychotic medications (at least represented by a proxy used in the study) [2]. Subsequently, the results of the CATIE study have been replicated in other large studies and in published meta-analyses. Since then, there have been additional new medications that have been approved by the regulatory agencies and introduced to clinical use, but these medications are largely variations on the same theme as were the second-generation and first-generation drugs that we used in the CATIE study. Therefore, the landscape, in terms of pharmacologic options for treating schizophrenia has become more vast, but has not really become much different or better than it previously was. I think it is not too harsh a statement to make that the field is at a plateau. I would not say stuck, but it has not really been able to move forward in terms of being able to identify a novel mechanism of action that is effective in the treatment of psychosis, or any of the associated symptoms of schizophrenia, and that has successfully guided new drug development. There is much research being conducted to develop drugs based on novel neurobiological targets and using novel mechanisms of action,

but we are still at the stage where these are hypothesis-driven and have not been definitively confirmed by proof-of-concept studies.

Q Could you briefly describe the aims of the two clinical trials: Lurasidone Cognitive Remediation Study and MEZO-QR that you are presently conducting?

At Columbia we have a large program in experimental therapeutics trying to develop new treatments or test new treatments that seem to hold promise in schizophrenia. These are aimed at testing compounds that have novel targets or mechanisms of action. We are also looking to refine treatments, how they are used and to more effectively manage side effects associated with standard pharmacologic treatments, as well as looking at the potential benefits of combining pharmacologic treatments. The Lurasidone Cognitive Remediation Study (LCRS) is studying patients on lurasidone, a new antipsychotic medication and the most recently approved by the US FDA for clinical use. It has a pharmacologic profile that is similar to many of the other newer antipsychotic medications: a moderate-to-low affinity to the dopamine D2 receptor and a higher affinity to the 5-HT_{2A} receptor, acting as an antagonist. The one distinctive property that may be clinically important is its higher affinity and selectivity for the 5-HT₇ receptor, a receptor that has been implicated in preclinical studies as influencing cognitive function. So in this study we are asking the question: if you treat patients with lurasidone – a drug which ostensibly can facilitate improvement in cognitive function, what are the potential added benefits of what has become a very popular type of adjunctive treatment called cognitive remediation? This is a treatment that is essentially a series of computer exercises for the brain geared to enhance specific cognitive functions. In this study, patients were all treated with lurasidone and then randomized to receive either cognitive remediation or some type of group treatment that does not specifically allow for these cognitive exercises to be performed. The question is whether cognitive remediation will improve cognition, so in this study we will be looking at the effects of this adjunctive treatment using lurasidone, a drug which may have some selected antipsychotic benefit.

The MEZO study is a study that really addresses how you manage the drug-induced side effects of weight gain and the metabolic syndrome. In the aftermath of CATIE, my colleagues and I were

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involved in carrying out a series of studies that attempted to address the question: what do you do if you are treating somebody who is doing reasonably well and exhibiting a therapeutic response but they have gained a lot of weight or they have been diagnosed as having metabolic syndrome? We have studied this question in three different ways. The first was a study called Comparison of Antipsychotics for Metabolic Problems (CAMP), which took patients who met criteria for the metabolic syndrome (i.e., excessive weight gain, raised blood glucose, blood pressure, triglycerides and cholesterol) and were on stable antipsychotic medication. We randomized them to stay on that medicine (olanzapine, quetiapine or risperidone) or switched them to aripiprazole, a drug that produces much less weight gain and metabolic effects than the second-generation antipsychotic drugs. The study was led by Scott Stroup and is currently being published, but essentially it found that administration of aripiprazole led to a gradual remission of the metabolic syndrome, indicating that this drug-induced condition was reversible [3].

The second study we conducted to address this question was the Metformin in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia (METS) study, and it took people who had metabolic syndrome or a BMI of 35, were stable on antipsychotic medication and randomized them to either receive metformin (up to 1500 mg per day) or a placebo added to their antipsychotic medication. The finding was that a minimum of 3 months of metformin resulted in a substantial reduction in weight of patients compared with those who were given the placebo, highlighting this as an effective strategy for managing weight gain. Now metformin has become commonly used and is often even given prophylactically when starting someone on weight-inducing antipsychotic medication, similar to the way anticholinergic medications are used with the older medicines to prevent extrapyramidal symptoms (EPS) from developing.

In the MEZO study, which is the third study, we are looking at the effect of switching to ziprasidone, which, like aripiprazole and lurasidone, has a lower propensity to cause weight gain and metabolic effects in patients. This again involves taking patients who have either metabolic syndrome or a BMI of 35, but who are, this time, randomized to be switched to ziprasidone or remain on their current medication. The goal is to determine the improvement in weight or

metabolic indices and this series of studies is really geared towards trying to manage the side effects as opposed to enhance the therapeutic effects of treatment.

Q You currently serve as Principal Investigator on the newly awarded NIMH contract Recovery After an Initial Schizophrenic Episode (RAISE). What are the main aims of this research project and how do you anticipate that it might impact on the future management of schizophrenia?

Well, as I mentioned before, for much of the history of psychiatry, the attitude was that we could not really do much to prevent the devastation of schizophrenia from occurring. That started to change in the late 1980s/early 1990s with the first episode and then prodromal studies that examined patients in the early stages of their illness, and demonstrated that the treatment response and outcomes were quite good if treatment was administered early, and that the earlier you were able to treat people, the better off they would be in terms of level of recovery and prognosis. That, combined with the imaging and neurobiological studies, suggested that early intervention could prevent the progressive pathophysiologic effects of the illness. This body of evidence reached a level, which suggested that it was ready to be applied to a service-delivery model that could be used on a widespread basis in mental health care systems. The NIMH recognized this, and they funded a project called Recovery After an Initial Schizophrenic Episode (RAISE) in order to have studies performed that could demonstrate application of this methodology in community-based settings with real-world patients in the first episode or beginning stages of their illness, and demonstrate that it can indeed improve outcomes and prevent these patients from progressing to disability, and not being able to return to their work or educational activities. So the NIMH funded two projects, which utilize complementary study designs, to be carried out and essentially prove this principle – this idea that intervention may result in improved recovery and prevent disability. If these are successful, this could provide the basis for a new model of mental health service delivery that could be rolled out for adoption by mental health care systems in the public and private sectors. The implications of this would be enormous because schizophrenia is a low incidence but high prevalence disease; that is, only a certain number of individuals will develop it in any given year

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but, generally, once you have got it, you have got it for life. If we enhance prevention by attacking the illness at its most vulnerable point (when treatment can be most effective) and prevent the morbidity from accruing and disability from developing, this will prevent this high prevalence disorder from becoming such a burden on a large number of people and so costly to society. This is a very exciting undertaking, and with the RAISE study we are at that point in the trajectory of scientific research when you can see a research finding being translated to clinical practice.

Q What are the most important questions that still need to be addressed in schizophrenia research?

There are really two main areas. Firstly, the early detection and intervention strategy has given great hope and momentum to our efforts to try and prevent the disability from developing, but that is not going to help people already in the advanced stages of their illness. Therefore, a critical area is to develop effective therapeutics for patients who are already in the chronic – what I would call the ‘pathologic end stage’ of the illness. These are probably not going to be treatments that are synaptic modulators that inhibit dopamine or glutamate, but are probably going to be treatments that simulate neurotrophic and neurogenetic effects, because we are trying to repair cells that have been damaged and enhance synaptic connections. We therefore need a new pharmacology that is really rehabilitative and regenerative. I think that this is a key area of research and it is an area of research that overlaps with neurodegenerative diseases and regenerative medicine. It could be that stem cells have a role in this or treatments that stimulate neurogenesis and trophic factors may have a role, but it is currently an underdeveloped area of pharmacology that needs to be pursued.

I think the other area is where the early detection/intervention movement has led us: to an awareness that schizophrenia, like many mental disorders, is an illness that has its origins in genetic liability and risk (i.e., there are vulnerability genes). What this means is that people who are at risk are potentially identifiable during the premorbid phase, even as early as infancy, but the problem is that the phenotype is not expressed and identifiable until much later. Thus, research is moving in a similar direction to that of the field of cardiovascular disease, where we will be able to identify various risk factors, including

genetic risk factors that can be identified in the premorbid period and then developing interventions or strategies that can reduce risk and prevent disease progression. In cardiovascular disease, if a person has a family history, high cholesterol or certain genetic factors they can be advised to modify their lifestyle, potentially take a statin drug, take aspirin or to do certain things to modify risk long before they ever experience symptoms of the illness. I think with schizophrenia and mental illness we would like to be in a similar situation where we can identify people’s risk in a quantifiably precise way and propose to them either treatments or behavioral modifications that can mitigate that risk. I think the field is going to end up going very much toward early identification of risk, then reduction of risk and prevention of illness. That is going to involve the use of genotyping and the use of various laboratory-based diagnostic methods, particular imaging and electrophysiological measures. We may also have the advent of proteomic-based measures that can provide us with some risk indicators as well, but I think between genetics, imaging, electrophysiology and potentially proteomic-based measures, we will have the capacity to evaluate people and provide them with some kind of quantitative risk assessment and then recommend strategies to mitigate that risk and prevent illness.

“...the early detection and intervention strategy has given great hope and momentum to our efforts to try and prevent the disability from developing, but that is not going to help people already in the advanced stages of their illness.”

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Jeffrey A Lieberman has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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