

**MARTIN M. KATZ: DEPRESSION AND DRUGS**  
**The Neurobehavioral Structure of a Psychological Storm.**  
**New York: Springer; 2013. (92 pages)**  
**Collated Document by Olaf Fjetland**

This collated document includes Martin M. Katz's monograph, "Depression and Drugs," posted on August 8, 2013, and the exchanges that followed the posting of this monograph.

Four participants exchanged a total of 26 postings: 13 by Martin M. Katz, 11 by Donald F. Klein and one posting each by Samuel Gershon and Per Bech. The last entry in this exchange was made on October 20, 2016.

It was only in November 2016, when the preparation of this collated document began that it was noted that Katz's reply to Klein's Second Comment was missing. When this was brought to Katz's attention he told us that he will prepare a reply. By that time he was seriously ill; he passed away on January 12, 2017.

This collated document is now open to all INHN members for final comment.

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| Martin M. Katz  | August 8, 2013     | review                                   |
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| Martin M. Katz  | September 12, 2013 | reply to Gershon's comment               |
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| Donald F. Klein | March 13, 2014    | 2 <sup>nd</sup> comment   |
| Donald F. Klein | June 12, 2014     | 3 <sup>rd</sup> comment/question  |
| Martin M. Katz  | July 17, 2014     | reply to Klein's 3 <sup>rd</sup> comment  |
| Donald F. Klein | September 4, 2014 | 4 <sup>th</sup> comment (mental syndromes and neurotransmitters)                      |
| Martin M. Katz  | October 23, 2014  | Reply to Klein's 4 <sup>th</sup> comment  |
| Donald F. Klein | November 13, 2014 | response to Katz's reply to 4 <sup>th</sup> comment                                   |
| Martin M. Katz  | December 11, 2014 | response to Klein's response to Katz's reply to Klein's 4 <sup>th</sup> comment       |
| Donald F. Klein | January 1, 2015   | response to Katz's reply to his 4 <sup>th</sup> comment and a 5 <sup>th</sup> comment |
| Martin M. Katz  | February 12, 2015 | reply to 5 <sup>th</sup> comment  |
| Donald F. Klein | April 2, 2015     | 6 <sup>th</sup> question/comment<br>Antidepressants are not stimulants                |
| Martin M. Katz  | May 7, 2015       | reply to Klein's 6 <sup>th</sup> comment  |
| Donald F. Klein | July 9, 2015      | 7 <sup>th</sup> comment   |
| Martin M. Katz  | October 8, 2015   | reply to Klein's 7 <sup>th</sup> comment  |
| Donald F. Klein | February 4, 2016  | 8 <sup>th</sup> comment   |
| Martin M. Katz  | April 28, 2016    | reply to Klein's 8 <sup>th</sup> comment  |
| Donald F. Klein | July 28, 2016     | final comment   |
| Martin M. Katz  | October 20, 2016  | reply to final comment  |

### **Martin M. Katz's Review**

**INFORMATION ON CONTENT:** The discovery in the early 1950's of the role of the central neurotransmitters and that of the new drug treatments for the mental disorders sparked a wave of research in the new science of neuropsychopharmacology. In the first two chapters, the book describes the impact of the new drugs on theory and research on the major depressive disorders, focusing on the interactions between neurochemistry and behavior and the role of diagnosis in clinical research. The author sets the stage for later detailing the misplaced reliance on diagnosis and introduces dimensional analysis to replace it in framing both basic and clinical research. In Chapter 3, "depression is a storm, not a lowering of spirit", he describes the psychological factors that have been seriously neglected in the burgeoning of recent neurochemical studies. He reports results of empirical studies of the clinical phenomena and the need to turn to literary artists who have been afflicted, to characterize the personal experience. Combining these approaches led to a new strategy of measurement. In Chapters 4 and 5 he describes the "Rashomon" approach to measuring the state, the "multivantaged method", and the resultant dimensions of anxiety-agitation-somatization, depressed mood-retardation, hostility-interpersonal sensitivity that represent the major part of the variance underlying its structure. Chapter 6, "False Assumptions," critiques the basis of most current drug research. Much of that work is guided by earlier misconceptions of the disorder and of the nature and timing of drug actions. New evidence contradicts these assumptions and cites a new path to research in this area. Chapter 7, "New Hypotheses", reports results from a follow up study that compared differently targeted antidepressants. It was designed to test hypotheses about drug actions derived from the earlier NIMH's Collaborative Depressive Study and to extend knowledge on how neurochemical and behavioral changes interact to resolve the disorder. Chapter 8, in describing a "more effective model for the clinical trial of new drugs," demonstrates the advantages of applying the dimensional conception of depression and the "componential" model, in place of the now 50 year old established "diagnostic" model, Finally, in Chapter 9, the author presents conclusions and describes a new theory about the nature of the depressive state, "the conflictual neurobehavioral state" hypothesis, a concept that views it as one of turmoil, not as unidimensional, but as one of conflicting central nervous system states, a "down, depressed retarded state" concurrent in the experience with an opposed "aroused, negatively excited,anxious" state.

**AUTHOR'S STATEMENT:** The book is a product of the author's experience in two major Collaborative studies of the Psychobiology of Depression that extended over a period of several decades. The themes covered ranged from results of basic studies which detail the specific relationships between central neurotransmitter systems, serotonergic and noradrenergic, and the elements of behavior, to a rethinking of the neurobehavioral concept of the disorder itself. Noting the neglect of behavior in more recent drug research it views depression, not as a singular disorder, but as comprised of multiple dimensions. It further recommends replacing the dominant role that diagnosis plays in framing most all clinical research with the dimensional profile. To achieve that goal, a new conception of the disorder is presented and a new strategy of measurement, the multivantaged method, as the framework for future research. The empirical results of two collaborative studies characterize the behavioral phenomena. The components of depression are then combined with the descriptions by literary artists of the actual experience of the disorder. These results lead to a re-conceptualization of how the drugs act to resolve the disorder, and a new theory as to the experience of the depressed state, based on the interaction of opposed neurobehavioral states. In introducing the new methodology the author seeks to change the approach to clinical trials. The established model, developed more than 50 years ago, is out dated and does not do justice to the many drug actions and forms in which the disorder is manifested. There is a Postscript. In the appendices, detailed descriptions are presented of the brief form of the *Multivantaged Assessment Method* and the newly developed *Video Interview Behavior Evaluation Scales (VIBES)*.

August 8, 2013

### **Samuel Gershon's Comment**

Dr. Katz's career was completely contemporaneous with the introduction of imipramine into psychiatry and was actively involved with most aspects of studies in the area of depression and its treatment and evaluation,. He was a primary player in the United States National Institute of Mental Health (NIMH) Collaborative Psychobiology of Depression Program launched in 1970 and ran for 10 years. He was involved in very many of the NIMH and United States Veterans Administration (VA) collaborative studies in these areas. This background together with his own research on the clinical assessment concerns about the methods and the approaches used for the evaluation of change caused him considerable concern, He then undertook methods to develop

new approaches that might present an evaluation of different facets of the clinical state. From his position he was perfectly situated to look at the data from all points of the compass, His conclusions offer the reader a very sobering picture of our current status of knowledge and he concludes we need to reevaluate our many positions and beliefs. He quotes a Collegium Internatinalne Neuro-Psychopharmacologicum (CINP) task force report "we still have found no biological 'markers' of the disorder nor are we completely clear as to mechanisms underlying their efficacy in depression" or their mode of action. He goes on to note the vast disparity in accumulated knowledge in genetics and neurosciences with the fact that no new compounds have been developed in the last 30 odd years. He feels that part of the problem may be in the central clinical problems in this area as well as the design and assessment aspects of the study He has spent many years of his own research in trying to address these questions. In conclusion the volume forces us to look at these discrepancies with these new approaches in mind,

August 15, 2013

### **Martin M. Katz's Reply Samuel Gershon's Comment**

Sam Gershon is one of the pioneers of psychopharmacology. I am pleased that he is in agreement with my current perspective on the state of research in the field and that he praises the contents of the book.

He and I are disturbed as are many researchers in clinical psychopharmacology, with the failure during the past three decades, to develop new classes of antidepressants. Through the kind of analyses and recommendations outlined in my book and the contributions of others in the field, we hope to encourage young investigators to rethink the nature and definition of the multi-dimensional depressive condition, and to be more innovative in uncovering the specific actions of established and new treatments.

A change in mind set on the disorders by psychiatry and the introduction of more efficient and less expensive methodology for clinical trials can stimulate the pharmaceutical companies to restart full operations in the development of new psychotropic agents.

September 12, 2013

## Per Bech's Comment

We all have to listen carefully when a psychologist has released a book on the treatment of depression with drugs. Even more so when the psychologist is Martin Katz who was executive secretary of the first advisory committee to Jonathan Cole's Psychopharmacology Service Centre in the USA in the late 1950s, and was director of the Laboratory of Experimental Psychology in Herman van Praag's Department of Psychiatry at Albert Einstein University in New York in the early 1990s.

The neurobehavioral approach to depression is described in this small and well-written book in which Martin Katz links the functioning of the serotonergic and noradrenergic neurotransmitter systems in the brain to different clinical components of depressive states. Katz's story is in a certain sense the opposite story to Arvid Carlsson's when identifying the functioning of these neurotransmitter systems. Carlsson was inspired by the work of the experienced psychiatrist, Paul Kielholz who found clomipramine to be the most potent mood activating tricyclic antidepressant and desipramine to be the most motor activating tricyclic antidepressant. Building on Kielholz's clinical findings Carlsson showed that the dual actions of these antidepressant drugs entailed an initial effect on serotonin reuptake inhibition and thereafter an effect on noradrenaline reuptake inhibition. Had Carlsson accepted the claims in many reviews that all antidepressants have the same therapeutic profile he would not have been able to discover what he did. In the same way, had Martin Katz followed meta-analytic findings he would not have discovered that the profile of clinical depression is a psychological storm, a state of psychological turmoil, a term he borrowed from William Styron's description of his own depressive illness in his book, *Darkness Visible*.

Using principal component analysis in clinical trials with both the Hamilton Depression Scale and the self-reported Symptom Checklist (SCL-90) Katz and his co-authors identified three components explaining 75% of the variance. The three components are: depressed mood, anxiety-arousal symptoms, including sleep, and hostility – interpersonal sensitivity.

Using these three components Katz compared the serotonin reuptake inhibitor paroxetine and the noradrenaline (norepinephrine) reuptake inhibitor desipramine in a placebo-controlled study. In patients who had a good clinical response it was possible to show within the first two

weeks of therapy that drugs acting on serotonin reuptake have an effect on anxiety as well as on hostility some days before their action on noradrenaline and depression.

On the basis of his findings Katz's recommendation to the industry is that clinical trials with new potential antidepressants need not last more than two weeks, and that the classical practice of relying only on the total score on the Hamilton Depression Scale might result in the throwing out of many good babies, good drugs, with the bathwater.

In 1994 Martin Katz asked in a paper whether we are doing the right thing when we are using the traditional meta-analytic studies with the total Hamilton score as outcome measure in clinical trials with antidepressants. Over the last two decades Katz has confirmed that using the total Hamilton score is wrong. His small book tells us how to perform clinical trials with antidepressants. All those who are searching to find new antidepressants with a more rapid mode of action than the ones in clinical use need to read his book - listen to the words of the wise.

September 19, 2013

### **Martin M. Katz's Reply to Per Bech's Comment**

It is difficult in a brief commentary to capture the main themes of a book in which the author attempts to rethink the nature of a major mental disorder and evaluate the impact of diverse new drug classes in its treatment. I have Per Bech to thank for grasping my intentions as well as the technical recommendations for changing the direction of research on the mechanisms of action of antidepressants. In linking the results of our experiments to the early ideas of the astute Paul Keilholz on how the drugs work clinically, and to the sequence of neurochemical actions uncovered by Carlsson, he provides a meaningful context for the observation that we are currently approaching research problems in this area in the wrong manner. Depression as Bech notes from our results, is multidimensional and agrees that we must cease relying so heavily on diagnosis in the structure of research in psychopharmacology. If we adopt the dimensional approach, it will have major effects on how we design clinical trials of new agents. It will also, hopefully, stimulate experimentation on agents with novel mechanisms, research that will restart development in an area that has uncovered no "new" classes of antidepressant drugs for several decades. Bech with his depth in the field of methodology places our work in the proper context

for psychopharmacology and reinforces the need to move ahead in drug discovery with a new concept of depression and a broader range of approaches to behavioral measurement.

November 14, 2013

### **Donald F. Klein's Introductory Comment**

Martin Katz' early entry into clinical psychopharmacology, his career at NIMH, his collaboration with Jim Maas in the ambitious National Institute of Mental Health (NIMH) Collaborative Psychobiology of Depression Program, followed by the Texas Study, provides the industrious background for this book.

Katz recognizes that therapeutic drug mechanisms remain unclear and that drug discovery efforts by pharmaceutical companies have stalled. He believes that his collaborative studies provide a way out of these doldrums.

Katz states, "In this book I describe the research approach, and the new findings that led to: (1) identifying the major mood, cognitive, and behavioral components of the multifaceted depressed state; (2) uncovering the dimensional structure of the disorder; (3) further elaboration of the psychological turmoil that defines the experiential state of depression; (4) proposing a new theory about its conflictual nature detailing the interaction of neurochemistry and behavior which comprise the state; and (5) describing the impact of the antidepressant (AD) drugs on behavior and chemistry, that is, the drug-specific actions on behavior, and the onset and sequence of clinical actions that precede recovery".

This would be a remarkable accomplishment for a 92-page book.

However, this reviewer found it problematic attempting to comment on the book because he could not clearly understand some of the text and he did not agree with some of the contents. Since clarification that is not clear and exposition of disagreements is of general interest, it was agreed that instead of making one general comment, the reviewer will present a series of comments, in the form of 12 critical questions prompted by the book that would open up an interactive scientific discussion between the reviewer and the author. Such a discussion with possible participation of INHN membership could get down to details and continue until each "critical question" is clarified or interaction becomes unproductive.



January 23, 2014

### **Martin M. Katz's Reply to Donald F. Klein's Introductory Comment**

As a proponent of viewing depression as a “psychobiological”, dimensional disorder, and the antidepressants as having multiple clinical actions associated with differential impact on its neurobehavioral components, I realize that a number of technical and methodological concerns are raised in my book about how research is conducted on these issues. Don Klein is aware of these issues and their application to clinical research, generally. He apparently plans to identify them and to open them for discussion. I look forward to a useful interchange on these matters and trust that other members of the Network will participate in the discussion.

February 13, 2014

### **Donald F. Klein's First Comment: Sample Size**

Katz states, “In this book I describe the research approach, and the new findings that led to: (1) identifying the major mood, cognitive, and behavioral components of the multifaceted depressed state; (2) uncovering the dimensional structure of the disorder; (3) further elaboration of the psychological turmoil that defines the experiential state of depression; (4) proposing a new theory about its conflictual nature detailing the interaction of neurochemistry and behavior which comprise the state; and (5) describing the impact of the antidepressant (AD) drugs on behavior and chemistry, that is, the drug-specific actions on behavior, and the onset and sequence of clinical actions that precede recovery” (p. viii).

Katz believes that adequate description of depression requires contributions from doctor observations, patient self-reports, psychomotor performance, nurse observations and video interviews coded by behavioral evaluation scales (p. 26-8). These observations are linked, in part, by factor analyses.

Katz's “constructs of the depressive disorder are based partly on phenomenological analyses from Grinker et al. (1961) and Kendell (1968) and, partly, on the result of factorial

analyses of data assembled from the one hundred four moderately to severely ill patients sampled across the six hospitals in the CDS. The constructs encompass affect or emotional components such as depressed mood, anxiety and anger, disturbed psychomotor performance, thinking, somatic functioning and social behavior elements. There are 11 components inter-correlated in various degrees that were factor-analyzed to derive fewer dimensions, independent in quality that could be applied to understanding the structure of the psychopathology underlying this class of disorder” (p. 26).

My general concern is that the sample sizes, a total of 106 patients, derived from six sites, are very small to serve as the bases for stable, generalizable factors. Further, the sample sizes seem to fluctuate. For instance, on p. 29 the sample is stated as 130.

Do you believe that this sample size is adequate for your purposes?

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Kendell RE. The Classification of Depressive Illnesses. London: Oxford University Press; 1968.

January 30, 2014

### **Martin M.Katz’s Reply to Donald F. Klein’s First Comment**

Sample size is always an issue in clinical research. The target sample in clinical studies is usually patients suffering from one of a range of mental disorders. When investigating a causal or structural factor in the makeup of the disorder or the effect of a treatment, the investigator strives to assemble a representative sample of the disorder – not easy to accomplish. Whatever the study results, however, they must be limited in their generality to the kinds of patients represented in the study. Second to representativeness of the sample, in accord with the study aims, is the consideration of sample size. Certain technologies to be applied to analyzing the

data require a minimum number of subjects so that not achieving a required size does not allow the statistical techniques appropriate to the problem to be applied. Factor analysis or principal components analyze the relationships among multiple variables. Depending on the precision with which these variables are measured, and the sheer number of variables at issue, factor analytic procedures require rather large samples to produce stable solutions. So, clinical research more so than basic research is burdened because of the complexity of its human subjects, the need to assemble large, diversified samples and to usually follow them over extended lengths of time. In evaluating the factors (dimensions), the viewer must take into account the content and quality of the methods utilized to derive them, and note, that in the end, their value is dependent on how well they meet the aims of the overall study.

The viewer will note that in the NIMH Collaborative Depression Study (CDS) (Maas et al 1980), the factors made possible the testing of neurobehavioral hypotheses and refined analyses of the drug actions upon the disorder. Their application resulted in new information about the composition of the disorder, about the timing and specificity of clinical actions of the drug, and of their associations with the underlying neurochemical changes affected by these drugs.

The problem initially confronting investigators in that study, based on the aims in the CDS of testing neurobehavioral hypotheses and the effects of treatment, referred to by Klein was to assemble a “representative” sample, diverse enough to cover the variations across the most severe of depressed patients. If such a group could be assembled and sound, psychometrically tested methods applied to the analysis of their psychopathology, it should be possible to uncover the essential mood, behavior and cognitive components that comprise the disorder. And then, through principal components analysis, identify the underlying dimensions that describe this structure.

How large and diverse a sample must be assembled to meet these aims? We note, as background, that because of the practical difficulties in this field noted, clinical studies usually progress on the shoulders of very small samples. So theoretical ideas, like the “catecholamine hypothesis” or the “dexamethasone test”, were developed from relatively small samples. The CDS sample in this area of research was designed to be especially large and diverse in order to generate more definitive tests of these hypotheses, originally developed on small samples.

Six hospitals in diverse areas of the country were recruited and representative samples of unipolar and bipolar depressives, selected utilizing the research diagnostic criteria (RDC), operational definitions of the disorders, resulted in 130 patients for this study, a “very large” sample in this sphere of research.

It was possible to use 73 of these patients for the second-order factor analysis of the behavioral components. The sample size requirements for factor analysis are based, as noted, on the number of variables, the soundness of the methods, so that 5 to 10 patients per variable is required for “exploratory” or confirmatory factor analyses (Floyd & Widaman 1995). The sample size used in the CDS study is not large for factor analysis (conducted with 11 variables) but adequate in accord with technical requirements. Probably more telling is that the variables included are not simply items, known to have dubious reliability, but are previously validated clusters of item score sub-factors already tested for reliability. The methods were selected based on prior factor and other analyses involving proposed dimensions of the disorder, uncovered in earlier research, and room was left in the analysis for the derivation of new 2<sup>nd</sup> order dimensions to appear in the new sample.

The principal components analysis is the most used, most precise technique available for such analyses. In evaluating the factors (dimensions), the viewer must take into account the quality of the methods used and note that in the end, the validities of the methods are dependent on prior psychometric analyses, and then on how well they do in meeting the aims of the overall study.

The viewer will note that the factors make possible the testing of the hypotheses, the refined analyses of drug actions on the disorder, resulting in new information about composition of the disorder, about the timing and specificity of clinical actions of the drugs, and their associations with the immediate neural changes effected by the drugs.

Of most importance, however, is that the analyses have made “visible” a conflict of opposed emotional dimensions in this disorder, which provides the basis for a new theory of its neurobehavioral dynamics. I expect, in the future, further elaborations on these dimensions and understanding of the “psychological storm” underlying the tumult and severity associated with this range of disorders.

References:

Floyd FJ, Widaman KF. Factor analysis in the development and refinement of clinical assessment instruments. *Psychological Assessment* 1995; 7: 286 - 99.

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March 6, 2014

### **Donald F. Klein's Second Comment: Concept of Depressive Disorder**

Katz states: "The constructs of the depressive disorder...encompass affect or emotional components such as depressed mood, anxiety and anger, disturbed psychomotor performance, thinking, somatic functioning and social behavior elements" (p. 26).

The goal was to "devise methods for measuring the psychological facets as separate elements". Eleven constructs were described, then boiled down by principal component analysis to three dimensions, referred to as (1) Anxiety-agitation-somatization-sleep disorder, (2) Depressed mood-motor retardation and (3) Hostility-interpersonal sensitivity (p. 35).

Katz argues that major depressive disorder should be viewed as multifaceted, rather than as a "whole disorder". The disorder comprises opposing central nervous system states...(p. 37).

Katz should clarify if he considers the term "depression" to refer to some single distinct class with multiple independent manifestations, like measles? Or perhaps to several symptomatically overlapping classes, like typhoid and typhus?

The Galenists saw the manifestations of illness as the particular, but entirely variable, combination of the four humors. Is that like the independent interactions of the opposing neurotransmitters? In contrast, Sydenham viewed disease as distinct in terms of phenomenology and course.

In particular, can Katz's primary statistical approach, factor analysis, resolve or deny the mixture problem: whether there are overlapping but distinct syndromes as opposed to a single syndrome with varying manifestations? Or, more drastically, whether both the mixture and

syndrome concepts are ill-advised? Is the proposed alternative that the conflictual interplay of independent components, neurotransmitters rather than humors, that generates symptomatic variety?

March 13, 2014

### **Donald F. Klein's Third Comment: Variations in Neurotransmitter Systems and Supervening Syndromes**

In Katz's view, do the several component neurotransmitter systems vary independently, producing all possible combinations and manifestations? In that case, there should be no recognizable syndromes or courses. Alternatively, are certain neurotransmitter deviation combinations particularly likely, thus giving the appearance of syndromes?

But if certain combinations of deviances are somehow favored, how does that differ from the diagnostic syndrome formulation, which accepts multi-causal impairments of a particular evolved adaptive function, as modified by adaptive backups, yielding a particular somewhat variable, syndrome?

June 12, 2014

### **Martin M. Katz's Reply to Donald F. Klein's Third Comment**

Dr. Klein raises basic questions concerning the neural mechanisms underlying the mental disorders, e.g., specifically, the depressive disorders and their relationships to our system of diagnosis.

“In Katz's view, do the several component neurotransmitter systems vary independently producing all possible combinations and manifestations? In that case, there should be no recognizable syndromes or courses. Alternatively, are certain neurotransmitter deviation combinations particularly likely, thus giving the appearance of syndromes?”

“But if certain combinations of deviances are somehow favored, how does that differ from the diagnostic syndrome formulation which accepts multi-causal impairments of a

particular evolved adaptive function, as modified by adaptive backups, yielding a particular somewhat variable syndrome?”

In responding, one has to acknowledge that such an analysis at this point in our progress is required at two levels, one, the presumed neurochemical basis for the mechanisms involved, and two, the observable behavioral and somatic manifestations of the disorders, which represent the sole indicators of the presence of the clinical syndromes. We understand that at this point in time, despite our knowledge of the role of genetics in the susceptibility to certain of these disorders, e.g., the bipolar disorder, we still have no “biological markers” for the diagnosis of any of the mental disorders.

Regarding the interaction of the central neurotransmitter systems at the first level, raised in Klein’s opening questions, there is evidence of strong linking in functioning among the dopaminergic, serotonergic and adrenergic systems, described earlier by Sulzer (1985) and later demonstrated in several studies, including in our own collaborative research program (Maas et al 1991). The intercorrelations are substantial, but do not approach unity, indicating that they do not vary together or completely independently, and thus, are not likely to “produce all possible combinations”. Evidence also exists that in attempting to link the dysfunction in the neurotransmitter systems to specific behaviors, as reported in the book by Katz (Katz 2013) and as summarized in the review by Morilak and Frazer (2005), the functioning of the serotonin system is significantly associated with “impulsive aggression” and anxiety and the norepinephrine system with motor retardation and depressed mood. There is no evidence that we are aware of what links a specific pattern of neurotransmitter dysfunction to a specific diagnosis. Progress along this line must await further advance in the capacity to link “diagnosis” on one side, to patterns of neurotransmitter dysfunction, on the other. Until then, Carlsson (2013) summed up our dilemma with his classic comment, “drugs don’t care about the boundaries between one diagnosis and another.”

I cannot adequately answer Klein’s second question, except to indicate that, at present, we do not appear to have the proper capacity. We are not able to link the two levels, that is, the neurochemical basis and an overt syndrome, directly. We are, however, part of the way, having established that the various neurotransmitter systems have distinct patterns of relationships with behavioral variables, such as anxiety, that are core aspects of most syndromes.

Basic clinical research that will adopt this behavioral componential approach in parallel with the elemental neurotransmitter systems, an approach discussed in detail in the “Depression” book, requires abandoning in this critical search, the established DSM diagnostic system. It is, however, more likely to enhance progress in uncovering the underlying biological patterns of the major dimensions of psychopathology.

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Sulzer F. (1985) The “serotonin-norepinephrine link hypothesis” of affective disorders. In: *Proceedings of the III World Congress of Psychiatry*, ed. P. Pichot, P Berner, K Thau. NY: Plenum Press, pp. 411-416.

July 17, 2014

### **Donalf F.Klein’s Fourth Comment: Mental syndromes and neurotransmitters**

If the neurotransmitters each control a particular behavioral domain, then particular distinctive arrays of behavior, such as melancholia, panic disorder, animal phobia, etc. (generally called syndromes), should each be mapped onto a particular complex of neurotransmitters. However, we are told that neurotransmitters vary without regard to any supervening syndrome. Does this imply that syndromes are due to some other non-neurotransmitter processes? Or, is it an argument for the lack of utility of the syndrome notion? Or, does it indicate that stating neurotransmitters vary without regard to supervening syndrome may be sometimes correct and sometimes wrong. I don’t see, given our current limited knowledge, how to decide. Perhaps, simply deferring judgment is the best option.



September 4, 2014

### **Martin M. Katz's Reply to Donald F. Klein's Fourth Comment**

Don Klein's question is: "if each neurotransmitter system controls a particular behavioral domain, then, distinctive arrays of behaviors (or syndromes) should each be mapped onto a particular complex of neurotransmitters?" But he says, "if neurotransmitter systems vary without regard to any supervening syndrome then syndromes are either due to other non-neurotransmitter processes or the syndrome notion is useless."

To respond to his question it is necessary to reexamine the background evidence of the relationships of the monoaminergic systems and behavior. There is no evidence currently that diagnostic syndromes are associated with any specific underlying pattern of dysfunctional neurotransmitter systems. The evidence shows, however, that each of the monoaminergic systems, dopaminergic, serotonergic (5-HT), and noradrenergic (NE) are associated with or regulate different, but potentially, overlapping patterns of behavior and mood. As summarized in the 2004 paper by Morilak and Frazer, 5-HT, is primarily associated with anxiety and impulsive aggression and NE with "arousal", mood and motor activity. Further, the neurotransmitter systems do not operate independently, but interact with each other, thus, complicating the nature of specific neurotransmitter-behavioral associations. There is no current evidence that neurotransmitter systems vary in accord with any clinical syndromes or diagnoses but disturbed patterns of behavior and mood that are identified as syndromes may yet be found to be associated with a pattern of dysfunctions in several of the neurotransmitter systems (Katz and Maas, 1994).

Applying this evidence to treatment issues, we note that because patients vary in their clinical profiles of the disorder, some, e.g., with peaks in anxiety, others with feelings of anger, it is possible and now done with some success, to select drug(s) in any given case based not on the diagnosis, but on the agent's targeted action on major behavioral component(s) of the disorder, i.e., the drug is selected because of its action on a specific neurotransmitter system or systems and that system's evidenced association with that behavioral component, e.g., an SSRI or a selective NE agent, a dual action, or possibly, an agent with a new pattern of specific clinical actions, expecting, through this pattern of associations, to achieve the most effective therapeutic result.

So, it is not yet clear whether a particular complex of neurotransmitters underlies any of the clinical syndromes. The evidence regarding the interactions of the neurotransmitter systems and behavior generally, and the soundness of the syndrome concept, however, point to the strong possibility that such patterns may well be eventually uncovered. What is needed to achieve an answer is to set aside the syndrome concept and to first apply in future neurobehavioral studies the same level of precision in describing the profile of psychopathology, i.e., the disturbed behavior, affect, and cognition associated with the syndrome that is applied to the measurement of the neurochemistry. Until then, we will have to, as Klein suggests, defer judgment on this important issue.

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October 23, 2014

### **Donald F. Klein's Response to Martin M Katz's Reply to His Fourth Comment**

Katz and I agree that it is best to defer judgment on the knotty area of syndromes, neurotransmitters, and distinct neurotransmitter behavioral effects while awaiting relevant findings.

During theoretical mysteries, various approaches are tried, hoping, as researchers do, that there may be a payoff.

Nonetheless, Katz clairvoyantly states: "What is needed...is to set aside the syndrome concept...first apply...the same level of precision in describing...psychopathology, applied to the measurement of the neurochemistry".

How can Katz be so sure about "What is needed"?

November 13, 2014

### **Martin M. Katz's Response to Donald F. Klein's Response to His Reply to Klein's Fourth Comment**

Don Klein states that we agree about “the need to defer judgment on syndromes, neurotransmitters and distinct behavioral effects while awaiting relevant findings.” We agree to a point. I, however, believe that we are further along on these issues than Don Klein may be ready to accept. The evidence is stronger regarding the differential associations the neurotransmitter systems have with behavior than many investigators acknowledge. Specific relationships of the functioning of the serotonin system and the regulation of anxiety and of “impulsive aggression” are strong, as are the norepinephrine system and its association with “arousal” and dopamine with motor activity (see Morilak, Frazer's 2004 summary of this basic research). True, the interaction among these neurotransmitter systems are, in themselves, complicated, so that there is still much to learn about how the regulatory activities on various moods and behaviors play out in the functioning organism. But I believe that one aspect of the issue is very clear and that is that decades of attempting to find direct, straightforward linkages of neurochemical systems with classical mental disorders, as defined in the DSM, or even with syndromes as more commonly defined, has been unsuccessful, leading to many blind alleys. As Arvid Carlsson put it earlier, in another investigatory framework, “Drugs don't care about the boundaries between one diagnosis and another.”

This is not to deny the values of the diagnostic system or that disorders such as schizophrenia or the affective disorders are not real. Decades of study make clear that these syndromes clearly exist in much the same form as they are described in the established literature. The problem is that they are as conceptions, too complex in nature, and too difficult to quantitate reliably, to be of any great value in uncovering the neurobehavioral mechanisms underlying abnormal behavior and the impact of drugs on these mechanisms. The late James Maas and I encountered this “diagnostic” obstacle in early work on the psychobiology of depression attempting to relate drug-induced neurochemical changes to changes in the composition of the disorders (Maas et al. 1991). Our solution then, when seeking to uncover underlying neurobehavioral mechanisms, was to adopt a more elemental approach in measuring the behavioral side, i.e., to substitute the use of behavioral components and the dimensions that

structured the disorders, for the disorders themselves, rather than attempting to find links between the neurochemical systems and the “whole” disorders. This line of thinking and the evidence for it was elaborated in more detail in my book.

So, Klein is correct that I feel strongly that a major “drag” on progress is our over reliance on diagnosis and syndromes in clinical investigations as against improving the precision of our measures of anxiety, anger, apathy in order to further chart the network of associations of the neurotransmitter systems and behavior. Uncovering parts of this network has already improved our capacity to resolve issues about the underlying mechanisms of psychopathology and broadening our knowledge about the nature and timing of specific actions of antidepressants. It is the evidence utilizing this dimensional approach that has stimulated new thinking and theory about how the depressive disorders are structured and how the drugs work to achieve clinical response. That evidence supports my view that efforts should continue to be concentrated on further elaborating the characteristics of these all important neurochemical-behavioral networks and their functions in the various mental disorders.

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December 11, 2014

**Donald F. Klein’s Response to Martin M. Katz’s Response to  
His Fourth Comment  
and  
Klein’s Fifth Comment: Atypical Depression**

To quote Marty Katz, "Don Klein's question is: if each neurotransmitter (nt) system controls a particular behavioral domain, then, distinctive arrays of behaviors (or syndromes) should each be mapped onto a particular complex of neurotransmitters." But he says, "if neurotransmitter systems vary without regard to any supervening syndrome then syndromes are either due to other non-neurotransmitter processes or the syndrome notion is useless".

Marty says with regard to my question: "To respond to his question it is necessary to re-examine the background evidence of the relationships of the monoaminergic systems and behavior....So it is not yet clear whether a particular complex of neurotransmitters underlies any of the clinical syndromes.....The evidence shows, however, that each of the various of the monoaminergic systems, dopaminergic, serotonergic (5-HT) and noradrenergic (NE) are associated with or regulate different, but potentially overlapping patterns of behavior and mood."

It is here that we deeply disagree. I do not think this belief is well supported. Most apparent is our disagreement regarding onset of anti-depressant action, since the various anti-depressants have their ultra-quick uptake blockade while the modal clinical response occurs weeks later. Further, how can one speak about serotonin effects when there are 14 serotonin receptors or NE effects when dopamine is taken up in frontal lobe NE receptors, etc.? The simple rheostatic view of regulating behavioral/affective action, up or down, in step with neurotransmitter concentration --without regard for the intricacies of pathophysiology-- seems wrong. Elsewhere, I have suggested that certain manifest syndromes are due to an impaired adaptive function --that there are a host of ways to impair a function so simple genetic linkages will not do and that for those syndromes marked by spontaneous remissions-- effective medication can also normalize a dysfunction--such as can be accomplished for impaired negative and positive feedback loops. We have emphasized this view in our texts and concisely in: Klein DF. Cybernetics, activation, and drug effect. *Acta Psychiatrica Scandinavica* 1988; 77: 126-137.

Further, Marty suggests, "What is needed to achieve an answer is to set aside the syndrome concept and to first apply in future neurobehavioral studies, the same level of precision in describing the profile of psychopathology, i.e., the disturbed behavior, affect, and cognition, associated with the syndrome that is applied to the measurement of the neurochemistry."

I agree with more detailed phenotypic description --but of who? Note Marty puts aside the syndrome concept but nevertheless describes the phenotypic description "associated with the syndrome". I believe the most striking evidence for the syndrome concept is the fact of spontaneous remission, which contradicts the notion of a simple aggregate of difficulties.

Note that the current NIMH RDoC template eschews the syndrome concept, "supporting dimensional assessments" without concern for the nature of the subjects --who may be normal children, aged folk, demented patients, depressives, those who happen to come into the clinic, etc. All will be dimensionally informative, affirming the presumptive structure of the current problematic granting assessments.

Is there an alternative to dimensional phenotypic or endophenotypic analysis? I believe so. Current parallel group placebo controlled studies, that indicate a medication is or is not effective are very FDA useful --but do not specify which patient requires medication to remit and maintain gains.

This is possible through intensive design, varying the dose of apparently effective medications while ascertaining fluctuations in benefit. This is described in detail in: Klein DF (2011) Causal Thinking for Objective Psychiatric Diagnostic Criteria. Shrout PE, Keyes K, Ornstein K (Eds) Causality and Psychopathology . New York City: Oxford University Press, pp 321-337.

Finally, a well accepted (DSM 4 & 5) notion is that under the general label of depression there is a subgroup with "atypical depression" manifestations, that have a differential onset (early), course (chronic but reactive), and vegetative (hypersomnia, hyperphagia, severe fatigue, rejection sensitivity) symptoms. Almost the converse of melancholia as described in: Stewart JW, McGrath PJ, Quitkin FM, Klein DF: Atypical depression: current status and relevance to melancholia. *Acta Psychiatr Scand* 115 (Suppl. 433): 58–71; 2007.

Strikingly, those with an adolescent onset or chronic course have a specific psychopharmacological response to MAOIs, but not to TCAs. Strangely, late onset patients with atypical features may respond equivalently well to TCAs or MAOIs.

MAOIs are supposed to inhibit the catabolism of many (NE, 5HT, Dopamine) neurotransmitters. How would "Atypical Depression" and MAOIs fit into Marty Katz's schema?

January 1, 2015

### **Martin M. Katz's reply to Donald F. Klein's Fifth Comment**

I will follow up Don Klein's added comments to my last reply regarding linkage between neurotransmitter effects and behavior changes, in a separate text. Here I respond to his fifth comment citing "atypical depression" as a special case that he believes undermines the value of the scheme of relationships I have described, and leaves open the question of how one explains the positive and specialized actions of monoamine oxidase inhibitors in its treatment. The "atypical" is a contrary form of depression, its symptoms very unlike the classic melancholia. The monoamine oxidase (MAO) inhibitor drugs, demonstrated to be effective for this category, specifically phenelzine, inhibit the catabolism of many neurotransmitters. How would these actions fit into my scheme? A simple answer is that it requires examination of the neurochemical and behavioral mechanisms operating in this framework. The pattern of associations between neurotransmitter actions and behavior is different in "atypical" depression, e.g., the dopaminergic system apparently plays a different role, than that found with typical depressions. Only new research could provide the entire answer. The new research would be a challenge and an investigator with the necessary resources might find this study worth doing. In sum, there is as yet no evidence that the syndromes or diagnoses are in themselves, associated with specific dysfunctional patterns in neurotransmitter systems, no "biological markers" of these clinical concepts. The evidence so far indicates that such associations if they exist, are still outside of our research grasp.

If I read between the lines from Klein's critique it appears that he is disturbed with the putting aside of traditional, tried and tested clinical concepts of syndrome and diagnosis, when seeking to uncover the mechanisms of effective drug action in the treatment of depression. I can assure him from my side of the problem that I respect these concepts and the efforts over these many years to increase their reliability and validity for application in clinical practice. But I am suggesting that the complexity of their nature and their resistance to quantification indicates that they are not yet suitable to insert into a research framework that is aimed at uncovering how the established drugs bring about their therapeutic actions. The scheme I set forth in my book

generates a conceptual approach to the understanding of the neurobiologic dynamics of the depressed state drawn from this type of analysis that identifies conflicting affective and motoric dimensions, the conflict between the “aroused” anxiety-agitated neurobehavioral and “depressed mood- motorically retarded” neurobehavioral states, as the basis of the inner turmoil and suffering associated with an acute episode of depression. This approach has already resulted in new evidence on drug action mechanisms and I believe that this “conflicting dimensions” conception of the depressed state will continue to provide a proper guideline for future advances in understanding depression and in uncovering the bases of drug efficacy.

February 12, 2015

### **Donald F. Klein’s Sixth Comment: Antidepressants Are Not Stimulants**

Katz has stated that basic research links neurotransmitter systems with the regulation of different behaviors and moods, serotonin with “impulsive aggression” and anxiety and norepinephrine with “arousal” and “motor activity”. See Katz's reply to Comment Three.

Also, it seems that Katz views neurotransmitter effects as rheostat modeled that more transmitter yields more activity and less transmitter yields less.

Yes, there is extensive evidence that antidepressants have little effect on normal subjects, except for side effects. Antidepressants do not make ordinary people happy, aroused or aggressive. There is no demand for them on the street as there is for cocaine. Their benefits may come from a normalizing interaction with a pathological state, rather than by modifying a normal reactivity. This cybernetic hypothesis is detailed with regard to feedback derangement in my response to Katz's reply to my fourth comment (1/1/15) It deserves discussion.

April 2, 2015

### **Martin M. Katz’s reply to Donald F. Klein’s Sixth Comment**

Donald Klein refers to my characterization in the book of the relationship of the functioning of the central monoamine neurotransmitter systems to the regulation of specific



behaviors and mood, and then cites the limitations of those relationships. My analysis was based on a network of findings in basic laboratory research assembled over the past several decades that show an increase in availability of serotonin in the central nervous system to be associated with impulsive aggression and with level of anxiety and an increase of norepinephrine associated with “arousal”. I did not, however, view these relationships as rheostatic in quality. We agree that there are limitations to these relationships of neural and behavioral functioning based on our knowledge that the antidepressants clearly decrease the aggressive impulse, anxiety and stimulate motor activity in a large number of patients suffering from a depressive or anxiety disorder, but apparently, do not function in the same manner in normal people. The antidepressants are more likely, as he states, to have little but adverse effects in their actions in healthy controls.

I, therefore, have no quarrel with his statement that the antidepressants, although having a stimulant-effect in many depressed patients, are not “stimulants”. It is clear that the still unsolved issue is the basis for this uneven relationship of neurotransmitter and behavioral functioning, i.e., the antidepressants’ “normalizing” actions in most categorically depressed or anxious patients against a background of the drugs’ producing relatively neutral or adverse actions in healthy normal controls. The issue is central to understanding the neurobehavioral mechanisms underlying the efficacy of the antidepressants and remains unresolved. If it can be solved, it offers great promise for important advances in this field. I strongly agree with Klein that this issue deserves greater discussion from our colleagues.

May 7, 2015

### **Donald F. Klein’s Seventh Comment: Effect of Antidepressants on Normal Subjects**

How does the lack of antidepressant effect on normal subjects fit in your schema?

Factor analyses are often misunderstood as producing evidence for discrete groups. However factors are not discriminants. Yet Katz ties changes in specific neurotransmitters to particular changes in behavioral factors. However, Morilak and Frazer (p. 208), cited by Katz as providing useful background present a more complex model to deal with apparent contradictions:

“For instance, how can drugs that selectively enhance the tonic activity of the serotonergic system, thought to exert a primarily inhibitory influence on behavioral reactivity, produce the same therapeutic effects as drugs that selectively enhance the tonic activity of the noradrenergic system, thought to exert a facilitatory effect on behavioral reactivity? Indeed, if NE facilitates behavioral reactivity and arousal, how can drugs that selectively enhance neurotransmission in this system improve anxiety, at least as they do when it occurs in concert with depression?” Morilak and Frazer present a complex argument involving inhibitory receptors on the afferent neurons to deal with such issues. The apparent value of the rheostat model seems to be predictability, if A goes up, B goes up. Predictability is not evident with this more complex model.

July 9, 2015

### **Martin M. Katz’s reply to Donald F. Klein’s Seventh comment**

Don Klein’s comment about factors not being discriminants aside, he will note that for the purposes of our study, we had to establish, through psychometric analyses, that the measures of the behavioral components central to our study are reliable and valid. In Katz et al 1984, we describe those psychometric studies and the results supporting the validities of the methods, as measures of the constructs.

His further question concerning mechanisms underlying efficacy of antidepressants, aims more directly at the core of the theory I proposed, at the conclusion of my book regarding the "neurobehavioral" nature of the depressive episode. Essentially, my research on mechanisms was preceded by a descriptive reanalysis of the behavior, emotions and cognitive quality of the acute depressive episode. That analysis was drawn from a study that utilized an array of established psychological methods to characterize a large, diverse sample of depressive disorders (Katz et al 1984).

The study concluded, based on that evidence, that the core distress and turmoil we observe in the depressive episode was not simply the traditionally accepted concept of a "down", motorically retarded, state (Katz 2013). The experience of the victim was, rather, the result of opposing internal CNS states, one state, “down”, or sedated, the other, an opposed state of

stimulation, of negative 'arousal', i.e., anxiety, and in many cases, including anger, as reflected in the affect, the somatic complaints and the motor agitation reported by patients. It was the concurrence in time of these apparently, opposed states that was at the heart of the turmoil and distress experienced by the patient.

In accord with that analysis, the literature was then examined on how and why different classes of pharmacologic agents are similarly effective in the majority of cases. With Alan Frazer and Charles Bowden, ideas were tested that indicated that the drugs were not specific for the disorder of "depression" as a whole, but were, in fact, effective, depending on their chemical composition, in reducing specific, key behavioral elements of the disorder, such as anxiety, feelings of anger and retardation of motor activity (Katz et al 1994, 2004). Therefore, in research, if one wants to advance understanding of mechanisms, we deemed it best to work with a dimensional or elemental, rather than "holistic", concept of the disorder.

From this approach, we learned that the antidepressant drug's effect on serotonin concentration was associated with reduction of specific behaviors or emotions, prior to influencing the "whole" disorder (Katz et al 1994), i.e., "inhibiting" behavior, as reflected in the earlier work by Linnoila et al (1983) that showed the 5-HT relationship in reducing "impulsive aggression" and in a series of studies that linked 5-HT with anxiety (summarized by Morilak & Frazer 2004). Contrarily, norepinephrine, as expected, was found to be associated with arousal and increased motor activity.

The neurobehavioral mechanisms underlying the beneficial effect of the "antidepressants" on the overall disorder then, at a more basic level, can be traced to the associations of the serotonergic and noradrenergic systems with specific components of behavior, components that figure significantly in the nature of the disorder itself, as against the drugs being specific to the "whole" disorder of depression.

I am aware that this conclusion does not completely resolve the issue that Klein raises. The serotonergic and noradrenergic transmitters do operate in isolation but they interact in their effects. The selective antidepressants, e.g, the selective norepinephrine reuptake inhibitors (SNRIs), do not target norepinephrine exclusively, but also have been shown to have some, if less potent effects on the serotonergic transmitters (Javors et al 2000).

Further, we note that Klein questions my interpretation of these results and argues that if these are the selective actions of the drugs, why do drugs with different selectivity targets across the neurotransmitter systems, presumably the SSRIs and SNRIs, result in the same overall efficacy in treatment-responsive patients? Here, he is apparently thinking similarly to the clinical practitioner, that depression is a disorder and regardless of which neural systems are targeted chemically by effective antidepressants, the result is the same, i.e., the patient gets better. True, but he is apparently ignoring, or is unaware of the results of studies, which clearly show that the therapeutic effect on the disorder, as a whole, is the result of underlying selective effects of the drugs on 5-HT or NE systems, that in turn, are selective in their behavioral effects and initially result in different patterns of behavioral and affect changes.

**The different classes of antidepressants, therefore, achieve efficacy in the overall disorder through different pathways, different patterns of behavioral and affect change.** This is best explicated in our 2004 study (Katz et al.), where we confirm the existence of these different pathways, earlier hypothesized by Kielholz (1968) and Carlsson (1976), and initially uncovered in our Katz et al (1987,1994) study. Efficacy of the disorder is, therefore, achieved as shown in our 2004 paper (Katz, Bowden, Frazer) at a deeper level, by neurobehavioral mechanisms underlying the effective drug actions, i.e., that representatives of different classes of drugs initially affect different patterns of behaviors - the SNRI, desipramine, primarily, reduces motor retardation, depressed mood and the SSRI, paroxetine, “calms” the state, reducing anxiety.

We were not the first to recognize that the tricyclics, “dual” action drugs, were impacting multiple behaviors before showing efficacy for the overall disorder (see early work by Kielholz). So, in fact, although both classes of drugs, the SSRIs and the SNRIs, can be effective in reducing the overall depressive state, they achieve that efficacious effect in different ways. Our earlier work (Katz, Maas 1994, Katz et al 1994) demonstrating the association of changes in CSF 5-HT and NE metabolites, provided the background for this result and the Texas study (2004) confirmed the earlier results. Somehow, however, the results of these studies are not registered by most clinical investigators, even ones as prominent and as experienced in the field as Don Klein. Further, he asks why would a drug that selectively targets the noradrenergic system, presumably DMI, improve anxiety, an arousal state, as it occurs in depression? There is no clear answer except that we are aware that the so-called selective drugs are not "purely" selective, that the two neurotransmitter systems interact and that, as Javors et al have shown, DMI did

significantly elevate 5-HT, possibly the source of the reduced anxiety, as well as NE in our 2004 study.

Why then, Klein asks, in another query, do they not show analogous effects in "normal" people, the so-called rheostat effect? It is a good question. I would have to answer that I do not know. It is a problem that could be profitably focused on in future studies.

As an aside, in concluding, it never ceases to amaze that on this issue that has evolved from research on mechanisms, dating back now several decades, there is such resistance to accepting the hard evidence showing the underlying associations of the central neurotransmitter systems to the regulation of different patterns of behavior and affect (summarized by Morilak, Frazer 2004), findings that, in turn, led to evidence that different classes of pharmacologic agents affect different behavioral components of the depressive disorder (Katz et al 2004). **And that these behavioral changes are the source of the therapeutic effect on the overall disorder.** Observation of the responsive patient post-treatment does make it appear to the clinician that the different drug classes have the same therapeutic action, when, in fact, evidence has shown that the sources of their therapeutic action are quite different.

I, personally, as I am sure would others, welcome further discussion of why this resistance exists to accepting this now, not new, evidence, that would move us more closely to understanding the mechanisms underlying effective and rapidly acting drugs. Integrating this information could re-stimulate thinking on the development of "novel" agents, theory about mechanisms and treatment practice in order to deal more effectively with this most prevalent of major mental disorders.

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October 8, 2015

### **Donald F. Klein's Eighth comment**

Does Katz accept that the rheostat model that he uses is oversimplified? If so, how does that impact his predictive statements regarding outcome?

Perhaps the most striking feature of the book is the claim that the usual clinical trial is far too long. Katz states that trials of 2 1/2 weeks would be as accurate and certainly much less expensive, and more practical, than the standard six weeks. He states (page 56), "a significant change in one dimension which occurs within the first week to 10 days is highly predictive of full response to a six-week treatment route with that drug". I do not think that can be accurate.

Marty Katz, in his response to my reply to Dr. Carlos Morra's comment, posted some relevant data to this concern. (See Martin M. Katz's response to Donald F. Klein's reply to Carlos Morra's comment in Martin M. Katz's Onset of Antidepressant Effect. *INHN Controversies* October 15, 2015).

February 4, 2016

### **Martin Katz's Reply to Donald F. Klein's Eighth Comment**

I believe I have replied to the substance of D. Klein's last comment in earlier notes as he so indicates. In this comment, he again finds it difficult to accept the accuracy of the prediction that change in one of the clinical dimensions within the first week to ten days of the treatment period, is highly associated with a full positive clinical response at outcome of a 6 week course of treatment. I can understand the skepticism but I was quoting from the logistic regression analysis in our paper in Katz et al 2004 (pg. 574), which showed for the desipramine-treated patients, a combination of sensitivity and specificity of 0.90 and 0.88, respectively, with only the depressive mood-motor retardation dimension as the independent change variable.

We acknowledge that this result was from a study having a modestly sized sample and the dimensional concept warrants re-testing using a larger sample and diverse drugs, but consider the 2004 study sound evidence for the likelihood that that prediction is a valid one. The result is supported by the fact that large sample studies which only utilized early improvement on the Hamilton Depression Scale, e.g., the Stassen et al and Szegedi et al studies, found similarly high associations between improvement at two weeks and positive clinical response at outcome. These studies had in common the finding of near certainty (>90%) that the treatment would fail if the patient showed no sign of improvement during this two weeks period.

All of these studies provide strong evidence that the two to three week trial is a more than viable option. My colleagues and I make a more detailed case for "shortening the trial" in the recently published Katz et al 2015 article.

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April 28, 2016

### Donald F. Klein's Final Comment

The requested 2X2 data layout, as presented in "Martin M. Katz's response to Donald F. Klein's reply to Carlos Morra's comment" (INHN Controversies 10.15.2015) presented in a parallel project (Martin M. Katz: Onset of antidepressant action) were insufficiently identified, as Leslie Morey agreed (Controversies 12.12.2015). The ambiguity is the uncertainty about data in which row of the table should be considered as early improvement.

Assuming early improvement refers to row 2, this table roughly agrees with Marty's statement that "70% of patients showing early improvement would go on to respond at 6 or 8 weeks".

| Hamilton Rating Scale |      |      |  |
|-----------------------|------|------|--|
| Late Response         |      |      |  |
|                       | <50% | >50% |  |
| Early Response <20%   | 15   | 2    |  |
| >20%                  | 8    | 25   |  |

Note, 33 are predicted to do well but only 27 (82%) actually did do well. Based on Marty's within drug analysis the drug is overvalued. That this is considered clinically significant, is arbitrary. Such a clinical judgment should be stipulated prior to the investigation.

One might be interested in the possibility that a very low pre-score would indicate a likely treatment shift. However, even better, such a score should allow a drug-free period of clinical watchful waiting.

The, hopefully predictive, correlation (0.6) between pre- and post-measures, accounting for 36% of the variance, is generally considered too low for predictive use.



Further problems remain. The "active drug" sample,  $N = 50$ , combines the Paroxetine study ( $N=24$ ) with the DMI study ( $N=26$ ). No justification is given. The combination of Paroxetine, picked as a serotonergic agent and DMI as a noradrenergic agent, requires a priori justification. Apparently an increase in sample size was considered necessary.

Marty provided placebo data used by Morey. This allows progress from a predictive study, derived entirely from within drug data, to an estimate derived from contrasting drug vs placebo.

|         | Drug | Placebo |
|---------|------|---------|
| Recover | 27   | 6       |
| Not Rec | 23   | 13      |

Chi-square = 2.77 Trend  $p=0.09$ , 2-Tailed

In any case, an analysis focused on invalidating the null hypothesis does not answer the question with sufficient strength to be a useful predictor. The correlation, 0.6 found here has 95% confidence limits of 0.39, 0.72.

So the upper limit of the correlation remains insufficient for predictive utility, even if one stacks the dice by an untrue assumption of sample bivariate normality.

Katz's argument is destroyed by the insignificant contrast between drug and placebo outcomes. Even strong findings, if derived from a small data set, would call for large sample replication before allowing interpretation as sound predictions about the useful length of definitive clinical trials.

That this insignificant, 6-week, drug vs. placebo contrast justifies the utility of a much shorter clinical trial is preposterous. Katz's claim that larger studies have already agreed with his conclusions needs more than an article reference. The exact analyses allowing parallel conclusions must be pointed out. I have failed to find them.

It is also illogical for large supposedly definitive trials to be followed by a small trial, that at best could add nothing new.

July 28, 2016

### **Martin M. Katz's reply to Donald F. Klein's Final Comment**

Don Klein's final comment on my book confines itself to a very small part of the case presented that early reactivity to antidepressant drug treatment, i.e., within two weeks, predicts outcome response in clinical trials. My case on this issue included reference to our Texas study which, although utilizing a moderately sized sample of drug-treated patients (n=50), demonstrated how early actions on specific behavioral components of the disorder could predict outcome (the study was designed to test hypotheses about drug actions), but the study within its limitations could not as we previously, pointed out, by itself, make the case. We cited the study evidence looking toward testing the prediction hypothesis in a "prospective" study that would include a significantly larger, and presumably, more representative sample of these diverse disorders. For this preliminary study, we enlarged the patient sample by combining the paroxetine and desipramine treated-subsamples as "antidepressants" to conduct this pilot trial of the predictability of the components. The best predictive model for the DMI treated patients had only the dimension of depressed mood-retardation after one week as the independent variable. It achieved a combination of sensitivity and specificity of 0.90 and 0.88, respectively (Katz et al 2004). The Texas study was, therefore, not intended to be a definitive study for shortening the trial period for antidepressants but simply to show the potential of this approach and provide the basis for the conduct of a large sample prospective study. I have no great argument with Klein on that as I and others, specifically L. Morey, have discussed and answered the criticism in earlier exchanges on the issue.

What is difficult to understand in Klein's critique is his use of his disagreement with the Texas study analysis to downplay the overwhelming evidence on this issue, the results of a large body of work, conducted over decades, in order to maintain his point of view that early reactivity as a predictor has not been proven. In the face of the evidence from other large sample studies with diverse antidepressants, proper placebo controls, and application of the established Hamilton Scale, studies such as Stassen et al (1997) and Szegedi et al (2009), in which 90% of patients who do not show any improvement after two weeks of treatment are almost certain to

not show improvement or clinical response at outcome. Other studies show 70% of the drug effect in treatment-responsive patients to occur in the first two weeks and that 70% of those who do show improvement at two weeks respond clinically at outcome. Certainly these studies conducted during the past three decades, provide in sum, clear results on this issue. They confirm that early reactivity in the form of early improvement by the end of two weeks, is highly associated with type of clinical outcome.

These studies are reviewed in some detail in my book and can be examined directly in the references provided. Either Don Klein has not actually read the Stassen et al, Szegedi et al, and Taylor et al (2004) papers or for other reasons, refused to accept the results or is simply in denial of the factual evidence here. It is somewhat of a mystery and may be to others who have followed this dialogue, that such an astute and experienced clinical investigator can decline to accept the established data here. I encourage the reader to examine the sources directly, in order to assess the validity of the “predictive” hypothesis.

It is important if we are to move ahead in research on clinical trials to consider alternative approaches, such as those elaborated in my recent book, *Clinical Trials of Antidepressants*, a follow-up to *Depression and Drugs*. The book is designed to apply the advances in understanding the disorder and the bases of drug action to the practice of clinical trials.

I thank the participants in this dialogue and Dr. Klein for their close attention to the issues and to the book.

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