Collated
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MARTIN M. KATZ: CLINICAL TRIALS OF ANTIDEPRESSANTS: HOW CHANGING THE MODEL CAN UNCOVER NEW, MORE EFFECTIVE MOLECULES (New York: Springer; 2016)

Collated Document by Olaf Fjetland

This collated document includes Martin M. Katz's review of his monograph, "Clinical Trials of Antidepressants: How Changing the Model Can Uncover New, More Effective Molecules," posted on February 25, 2016, and the exchanges that followed the posting of this review.

Four participants exchanged a total of seven postings: four postings by Martin M. Katz and one posting each by Per Bech, Malcolm Lader and Walter A. Brown. The last entry in this exchange was made on July 28, 2016.

Martin M. Katz passed away January 12, 2017, and to close the exchange, this collated document is now open to all INHN members for final comment.

Katz	February 25, 2016	review
Bech	May 26, 2016	comment
Katz	July 14, 2016	Reply to Bech´s comment
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Martin M. Katz: Clinical Trials of Antidepressants: How Changing the Model Can Uncover New, More Effective Molecules (New York: Springer; 2016)

Reviewed by Martin M. Katz

INFORMATION ON CONTENT: This brief book makes note of recent failures and abandonment by many companies of antidepressant drug development. It takes current clinical trial protocols to task and replaces them with a contemporary framework for improving next-generation antidepressants and their underlying science. New, innovative models are based on a neurobehaviorally-informed understanding of drug mechanisms and the component cognitive, mood, and behavioral aspects of depression. The book reconceptualizes not only the clinical trial process but the clinical concept of depression itself, from a "holistic" to a "dimensional" model. These changes are essential to bring pharmaceutical research and development up to date, in order to boost efficiency and effectiveness in finding new molecules, and reducing waste. In proposing a new theory of depression, it brings decades of research on onset and specificity of dug actions current, illustrating the application of the new models with case studies and a review of salient depression methods. It is a follow-up to the author's earlier, more conceptionally-oriented treatment of the subject in his book, *Depression and Drugs* (Springer, 2013), demonstrating the potential benefits of such wide-scale change.

Included in the coverage:

- Why now the need for a new clinical trials model for antidepressants?
- Aims and basic requirements of clinical trials: conventional and component-specific models.
- Methods for measuring the components and the profile of drug actions: the multivantaged and video approaches.
- Achieving the ideal clinical trial: an example of the merged componential and established models.
- Prediction and shortening the clinical trial.
- The video clinical trial.

AUTHOR"S COMMENT: This new book was designed to follow-up the author's earlier treatise: *Depression and Drugs: The Neurobehavioral Structure of a Psychological Storm* (Springer, 2013). It is intended, in part, to apply the principles, the new theory of "opposed neurobehavioral states" and the methodology developed to test that theory and to manage the thorny problems associated with the evaluation of new putative antidepressants. The multivantaged (MV) and video models for evaluation are described in the first book and illustrated in more detail in the new presentation, complete with case studies so that the reader can more easily follow the procedures. It is hoped that these "new" models can advance the science and introduce greater efficiency into the trial process, thus, encouraging the development of more effective and more rapidly-acting drugs.

February 25, 2016

Per Bech's comment

Although the pharmacological industries have doubled their research funds since 1991 for identifying new drugs with an antidepressant action more efficacious than the existing antidepressants, no such new drugs have been marketed. This is the background for Martin Katz' description of how his model can uncover new, more effective molecules.

The FDA requirements focusing on optimal dosage and marketability are referred to by Katz as an applied science, whereas his new model is a component-specific model in which the clinical trial becomes a potential step in facilitating an advance to finding new and more effective treatments of major depression. Thus, according to Katz, antidepressants are not "diagnosis-specific", but are in their modes of action "component-specific". He refers, in this respect, to Hotelling's principal component analysis by which he has identified such components as depressed mood, psychic anxiety, psychomotor retardation, psychomotor agitation, hostility, somatization, interpersonal sensitivity, sleep, or cognitive impairment. These components can then be parts of specific dimensions, namely (1) anxiety-agitation-somatization-sleep; (2) depressed mood-retardation; and (3) hostility-interpersonal sensitivity. At the item level of these

dimensions, Katz predominantly refers to the Hamilton Depression Scale (HAM-D) and the Symptom (SCL-90).

From a clinimetric point of view, it is indeed valid to have these two rating scales as the platform for the component/dimensional specific approach. The time has come to use both the HAM-D and the SCL-90 as multidimensional scales and not within the concept of the traditional FDA guided trials where these scales are "bureaucratically" considered as unidimensional. The total scores of the HAM-D or the SCL-90 are not sufficient statistics when using Katz' model for the identification of new, more effective molecules.

Throughout his new book, Katz has used his previous placebo-controlled trials with desipramine versus paroxetine to demonstrate the onset of action for the componential approach, illustrating the superiority of desipramine on the dimension of depressed mood- retardation, with an onset of action already after 3 days compared to 13 days for paroxetine and 21 days for placebo. From an economic standpoint, when performing clinical trials of antidepressants, Katz recommends such intensive assessments of specific drug-induced changes. He concludes that the field of neuropsychopharmacology stands to gain new knowledge of importance to both basic and clinical research.

We all must read Martin Katz' attempt to educate us about his very impressive work on going beyond the FDA model of applied science to the basic science of clinical psychopharmacology.

May 26, 2016

Martin M. Katz's reply to Per Bech's comment

Per Bech captures the main issue in the book, and fully endorses the need to extend the assessment of drug actions in clinical trials to include the componential, dimensional approach. Bech who sharpened the Hamilton Rating Scale to make it even more effective in clinical trials is aware of that scale's strengths and limitations and strongly supports my multifaceted approach to the problem. He is one of the leading authorities in psychopharmacology in Europe, well in touch with how clinical trials are conducted throughout the pharmaceutical industry on both continents. I thank him for

support of my efforts to encourage the field to broaden the assessment effort in these trials and to render them more productive in seeking, new, more effective molecules.

July 14, 2016

Malcolm Lader's comment

Martin Katz is a psychologist with a distinguished record in psychopharmacological research. In this book of exemplary succinctness, he concentrates on the FDA requirements for efficacy trials for antidepressants. He is particularly critical of the wasteful nature of these trials and the limited conclusions that can be drawn. The Hamilton Depression Scale is a particular bête noire (Hamilton, 1960). My comments are primarily designed to stimulate controversy and initiate a discussion. Thankfully, as a European I do not have to comply with the rigid, almost ossified, FDA regulations. I have those of the EMA instead!

I shall consider some general points first. What is the purpose of an efficacy trial of this sort? It is basically a *legal* procedure to establish efficacy according to pre-set, usually legislative criteria. The outcome variable may be specified as, for example, a proportional drop in the Hamilton Depression Scale Score. But this is an artificial outcome. The practising clinician actually relies on a probabilistic analysis of the chance of obtaining a useful therapeutic response in her/his patients as compared with other treatments, both pharmacological and non-pharmacological. In clinical practice this therapeutic response is a pragmatic outcome such as discharge from hospital or outpatient clinic (e.g., Keller, 2003). Furthermore, in conjunction with the efficacy, it is essential that the risks of the treatment are carefully evaluated so that a proper risk-benefit ratio can be estimated (Friedman and Leon, 2007). Such profiles usually need much larger numbers than for an efficacy trial particularly if the profile of adverse effects contains some rare but severe, even life-threatening, reactions. Post-marketing surveillance may be needed to fulfil that role. In addition, the clinician will have calibrated this risk-benefit ratio against the severity of the condition that he is treating, accepting greater risks for a more severe indication. He may conclude that the risks outweigh the benefits in all but the most severe of the the patients who seek help. Also a differential response in some

patients needs careful evaluation so that a particularly responsive sub-type can be identified.

Severity is an important dimension that regulatory authorities may overlook or delegate to cost-effective assessments. As a general rule it is easiest to establish efficacy in the most severely ill patients such as those with a Hamilton Score in the 30s or a MADRS of at least 30 or even 35 (Montgomery and Asberg, 1979; Thase, 2011). Too often because of the exigencies of being able to recruit patients at an adequate rate, quite mildly ill patients are included and those may not show an adequate response.

One factor which is overlooked in this book is that most cases of unipolar depression have a self-limiting time span (Spijker et al., 2002). Natural remission is the rule rather than the exception. This raises practical problems - if the trial goes on for too long, say over 12 weeks, natural remission in the placebo group will obfuscate the improvement in the drug-treated patients. The theoretical way to control for this is to have a non-treatment group but this raises major practical and ethical problems.

Katz inveighs against the wasteful nature of the trials carried out under FDA auspices. I entirely agree with the waste of expensive resources but also question whether trials with such limited results can be truly ethical. Patients are being exposed to untried treatment procedures for a limited and over-focussed return.

One glaring example of this waste of patients and resources concerns the offset of action of putative antidepressants. A pharmaceutical company has a responsibility, scientific and moral, not to introduce any new medication to the market until it has been shown that the medication can be discontinued at the end of treatment with impunity or with only minor perturbations. The placebo-controlled trial provides an appropriate framework in which to establish whether cessation of treatment is uneventful, attended by a few symptoms, or by a recognisable and troublesome withdrawal reaction (Wilson and Lader, 2015).

Another neglected topic is compliance which can vitiate the usefulness of an efficacious compound (Demyttenaere and Haddad, 2000).

Katz implies that the FDA-type trial could fulfil 2 main goals. It can establish efficacy for registration purposes and it could be used for more widely useful scientific purposes. I believe that he is right that opportunities are lost but essentially he is asking for scientific studies into antidepressants to be carried out in a controlled context, a laudable aim. Unfortunately, this cannot be achieved in the controlled trials before

efficacy is actually established. Otherwise, if the candidate antidepressant proves inefficacious, much time, effort, and ethical credibility will be lost trying to elucidate the other aspects of the psychopharmacology such as biochemical changes. Caution is needed not to substitute one source of waste with another. I am also less enthusiastic than Katz in accepting correlations between antidepressant effects and biochemical changes. The relationships probably hold for norepinephrine (and I think dopamine) and motor activity, and between serotonin and anxiety, but I am less convinced that the biochemical correlates of depression itself are firmly established. To suggest that they could form the basis of a new model and thereby act as surrogate markers for clinical depression is surely an over-simplification. Correlations appear stronger with adverse effects than wanted effects (e.g., Gelder et al, 2009).

I would also urge evaluation of correlates of insomnia which is not only a common concomitant of depression but a notable harbinger (Benca and Peterson, 2008).

Katz adduces a small study from his own group to bolster his support of the different model of depression. I am concerned that he uses a circular argument when he states that his sample were “soundly diagnosed” as depressed. This merely means that the investigators came to some consensus on empirically derived criteria à la current DSM. He also falls back on the weak argument that it is “common knowledge” that a high level of anxiety accompanies depression and retardation. This is too facile. The approach needed in this argument is a return to first principles by carrying out a large study on a *populati*on sample with no preconceived assumptions about psychopathological categories. But I do think that the categorical approach merely serves to establish reimbursement criteria for health insurance agencies.

Katz takes particular issue with the Hamilton Depression Scale. It is a poor creature, indeed, with insensitive items. I once gently chided Max Hamilton – one did confront him trenchantly – about the Scale. He generously admitted that it had been drawn up hastily from text-book descriptions and had not been adequately tested for reliability and validity. Max regarded his Anxiety Scale as superior, and so do I. In fact, the MADRS generally seems superior to the Hamilton for rating changes in depression severity (Carmody et al, 2006).

In conclusion, I heartily support Katz’s criticisms and his plea for a new approach that maximises the biological factors. But I do not think that this constitutes a new model. Certainly more can be achieved and Katz points the way. But I am not fully

convinced that we know enough as yet for the alternative model to prove successful in the search for new medications. We are still caught in the Laocoönian coils of serendipity in the history of antidepressant discovery.

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June 23, 2016

Martin M. Katz's reply to Malcolm Lader's comment

Malcolm Lader is well known in British and European psychiatry and psychopharmacology having contributed substantially to the literature on clinical trials. He is in accord with the author's criticisms of the FDA model for evaluating antidepressants and broadens that critique to include the wasteful aspects and the "limited conclusions that can be drawn" from such trials. He is in agreement that although the Hamilton Depression Rating Scale has turned out to be a very important instrument for standardizing the measurement of efficacy, he turns to his personal experience with Professor Hamilton and the method to cite his reservations about its methodologic inadequacies. Dr. Lader also takes the opportunity to identify other problems to which the FDA presumably has not attended, e.g., allowing trials with ineffective drugs to go on too long, thus, further jeopardizing patient health, not following up with sufficient time to detect potentially serious withdrawal effects, etc. He is also critical of the author's evidence on correlations between clinical and biochemical effects, accepting some of these results, not others. Lader has a point that the correlational evidence is far from overwhelming but at the same time is, within its limitations, sound, and in my view, a highly useful step toward uncovering the complex interactive relationships between behavior and chemistry that characterize this neurobehavioral syndrome and that underlie the efficacy of the antidepressant agents. M. Lader, although supportive of the general

approach and the new models proposed by the author, is not convinced through his cursory analysis of their background, that we know enough about these methods as vehicles for finding new antidepressants. He is, however, prepared, to await further developments in clinical trials research. One direct way in which that can be accomplished is for investigators to begin to apply these proposed, well researched alternative methods in more studies

July 28, 2016

Walter A. Brown's comment

Although in the past 50 years both the US federal government and the pharmaceutical industry have spent billions of dollars seeking new treatments for mental illness, clinicians and researchers agree that no truly novel psychotropic drug has surfaced over this time. The key point here is novel.

Antidepressants are a case in point. The pharmaceutical industry comes up with "new" antidepressants all the time and they are launched with great fanfare. But these "new" antidepressants are invariably me-too variants of older drugs. In some instances, the antidepressants now in use have fewer side effects than the older ones but they are no more effective. And the newer antidepressants share many of the limitations of their forbears. Like the first antidepressants, the newer ones take several weeks to exert their full effects and they are ineffective in a large proportion of patients. The psychiatric community has acknowledged this lack of treatment innovation as a major problem. Although some of the reasons for the absence of innovation have been identified, the remedy is far from clear.

First, as many have lamented, despite great advances in our understanding of the brain, little is known about the specific brain abnormalities giving rise to depression. Thus, there are no obvious targets for which to design new antidepressants. As a result, pharmaceutical companies -a major source of treatment innovation- search for potentially useful "new" drugs by looking for compounds which are similar in structure or effects to the existing ones. This approach does identify drugs which work about as well as the existing ones (me-too drugs) but it can only fail with respect to innovation.

In addition, as Martin Katz suggests in this persuasive monograph, even if a researcher has in hand a compound with novel psychotropic properties, our current

system for evaluating psychotropic drugs makes it unlikely that its novel clinical effects would be detected, particularly if they were unexpected.

Mindful of the impediments to new antidepressant development and the high failure rate of contemporary antidepressant clinical trials (only about half the trials of approved antidepressants show them to be significantly better than placebo), Katz tackles several features of clinical trials methodology with an eye toward improving the success, efficiency and scientific value of those trials.

There's a good bit of wisdom in this brief (66 page) volume. Katz argues, convincingly, that since clinical trials are time consuming and expensive it makes sense to maximize the information that they provide. Instead of the current practice of evaluating outcome simply by the change in total score on a measure of depression severity, like the HAM-D or MADRS, Katz suggests that in addition to assessing changes in the depressive syndrome as a whole, efficacy studies should also include thorough measurement of the individual components of depression-anxiety, motor retardation, hostility and so forth. Katz points out that analysis of components provides more information on a drug's spectrum of action and would foster a better understanding of the relationship between a drug's pharmacologic activity and its behavioral effects. A clinical trial thus modified would go beyond a strictly commercial venture and advance the science of psychopharmacology. In some instances analysis of components might point to a symptom of depression that is particularly responsive to an experimental drug and thus rescue an otherwise failed trial. If this approach had been followed in the first trials of SSRIs their value as anxiolytics would have been discovered far earlier.

I agree wholeheartedly with Katz's idea that the information provided by clinical trials and their scientific value would be enhanced by a components analysis. But I would take his concept of maximizing information a bit further. Let's not forget that the antidepressant activity of the very first antidepressants, imipramine and iproniazid, was discovered when they were being studied for other conditions; imipramine was first tried in patients with schizophrenia (a few got hypomanic and a few showed a reduction in depressive symptoms) and iproniazid induced euphoria in some of the tubercular patients who got it. It's difficult to deliberately court serendipity, but clinical trials could incorporate, as a matter of policy, an open minded stance to clinical effects, frequent, meticulous and extensive clinical observation and attention to and follow up of unexpected clinical changes.

Katz also points to data from his own and others' studies that challenge the widely held belief that it takes several weeks of antidepressant treatment before improvement occurs. He shows that much of the symptom relief brought by antidepressants comes in the first two weeks of treatment and that the type of early response predicts response later down the line. Notably, the absence of improvement in the first two weeks is highly predictive of lack of response at six weeks. Clinical trials could be less costly and time consuming, Katz suggests, if they were shortened on the basis of early response. Although early response can be detected with conventional severity ratings on the HAM-D, Katz's work suggests that measurements of components are more sensitive to early clinical change. He points out that prospective studies are required to pin down the relationship between early changes in depressive components and eventual outcome. Such studies would, needless to say, provide information pertinent to clinical practice as well as clinical trial design.

Katz's final recommendation is to use central ratings of videotaped interviews to assess patients in clinical trials. He provides a number of arguments for the value of this approach in multicenter trials, including reduction of variability among sites and raters, an enhanced capacity to observe and evaluate nonverbal behavior (Katz maintains that it's esier for one observing the interview than one conducting the interview to assess such behavior) and the capacity to establish an archive of taped interviews for further study. These proposed advantages of video based ratings make sense on intuitive grounds, and Katz points to data generated by him and his colleagues that suggest these ratings are reliable and more sensitive to clinical change than conventional ratings. Nevertheless, given the logistical hurdles and expense of this approach, data showing conclusively that it provides an advantage in reliability, validity and outcome is required before implementation is warranted.

Katz gives a nod to Ketamine, but throughout his book he refers to monoaminergic systems, serotonin, norepinephrine and neurotransmitters as providing the neurophysiologic basis for both depressive symptoms and drug actions. Given the ever vanishing validity of the monoamine hypothesis, this book would rest on firmer ground if it stuck to psychopathology and eschewed unproven neurochemistry. As Katz says: "The essence of what is proposed here is that we convert the 'clinical trial' into a 'scientific, clinical study' aimed at achieving both the practical, primary aim of determining whether the new drug is efficacious for the targeted disorder, and the

secondary scientific aims of describing the nature and timing of the full range of clinical actions the drug has on the major aspects of the depressive disorder.” This conversion can be accomplished without recourse to pathophysiological theories.

A few spots need copyediting. There are some useful appendices, including one which lists the instruments used to measure the depressive components.

July 7, 2016

Martin M. Katz’s reply to Walter Brow’s comment

Walter Brown, a highly experienced figure in the clinical trials field provides a detailed analysis of the book and a sharp, well thought through review of its contents. He points to the failure of the drug industry to come up with novel drugs and the slow pace in uncovering the "little-known specific brain abnormalities" that underlie depression. The monograph he states is persuasive in citing that even if new effects of a trial drug were present, the current model trial, is expensive and wasteful, and not designed to uncover them. Confining assessment to one depression scale prevents possible specific effects on particular symptoms, like anxiety, anything novel in the drug's effects, in other words, from being detected. He understands that such studies if they applied a componential approach, would provide a "spectrum of drug actions", not available in the current model. He cites the new models’ strengths in clarifying onset of clinical action, in predicting outcome from early reactions to drugs, and the potential for shortening such trials. Regarding limitations, although impressed with the early results reported utilizing the video approach, he is somewhat reluctant to see it applied generally before further data on validity is produced. Also, believing that the "validity of the monoamine hypothesis of drug efficacy is slowly vanishing", he suggests the author stick to psychopathology, until there is more clarity concerning neurochemical mechanisms in this area. In summary, the author agrees that results linking behavioral and neurochemical factors are only starting to be uncovered but believes that this area of research is farther along than Brown acknowledges. Nevertheless, W. Brown sees much to gain by the field attending seriously to the book's proposed changes in the clinical trials model, and provides an excellent overview of its content

July 21, 2016