

Books

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## Martin M. Katz: Depression and Drugs

### **Martin M. Katz's reply to Donald F. Klein's 7<sup>th</sup> 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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