

Chapter 2

Uncovering the Interaction of Chemistry and Behavior in Depression: The Dimensional Versus Diagnostic Approaches in Structuring Research

To uncover the nature of the depressive disorder and how the antidepressant drugs work, it was clear that intensive analysis of both the neurochemical structure and the types of changes in the behavioral and emotional state induced by this class of drug must be pursued. Thanks to the rapid development of methodology in neurochemistry, literally thousands of studies have been conducted which explore the neurochemical effects of the antidepressant drugs. We must also, however, have comparably sound methods for measuring effects on psychological functions.

This latter area of methodology is not as strong as one would like. The tendency in psychopharmacology has been to avoid this issue, to lean heavily on another model for assessing the behavior, one more congenial to medicine. The nature of this affective and cognitive disorder is, therefore, encapsulated in a “diagnosis” that simply requires certain criteria to be met in some cases, regardless of the relative intensity of the psychological elements and their interaction. The application of the diagnostic classification system (DSM-IV) bypasses the need to delineate the behavioral, cognitive, and affective components that comprise the disorder, simply requiring that certain symptomatic criteria be met. It is a way of foregoing the necessity to quantify the intensity of the various elements and the differing patterns of disturbed functions that characterize the many ways in which the overall disorder is manifested. The behavioral, affective, and cognitive components of the disorder are then downplayed in importance by viewing them as symptoms, as highly variable and relatively minor aspects of the whole disorder.

The problem with conceptualizing depression as a “whole,” rather than as a multifaceted disorder composed of behavioral and affective dimensions, is the source of the problem. The downplaying of the behavioral components as relatively minor aspects contributed to blocking the view of the nature of the disorder and the mechanisms whereby “neurobehavioral” changes are induced by drugs. The diagnostic approach has, therefore, impeded progress in the further understanding of its neurobehavioral nature and in determining how the drugs work. Consequently, use of diagnosis to structure clinical studies has stemmed the probable development of

new more effective, more rapidly acting antidepressants. The studies to be focused on in subsequent chapters adopt another model of study, the “dimensional” or componential, and hopefully avoid the problems that the diagnostic model creates [1]. The results of these studies permit intensive re-examination of the elements and the psychological structure of the disorder and a more precise analysis of the impact of the drugs, relative to the timing and nature of changes in the major components.

We discussed this conceptual issue in detail and how the diagnostic model can obstruct acquiring a clear view of the mechanisms underlying change in Katz and Maas [2]. In that paper, we provided a fuller discussion of the role the diagnostic model has played in this area. But suffice it to say that although the classification system provides a broad, practical framework within which to work, it defines depression too narrowly. The use of this overall “diagnosis” in research as a substitute for serious articulation of its behavioral component and mood components impedes progress in uncovering the neurobehavioral mechanisms which characterize its structure. It, therefore, contributes to delaying determination of the underlying causes of the disorder [3].

The introduction of highly effective drugs that appeared to be specific to the treatment of depressive disorders in the late 1950s followed closely on other major findings concerning neuronal transmission in the central nervous system. In 1953, norepinephrine and serotonin were found to be present in the brain leading to the then novel hypothesis that neurons communicated not solely through “electrical” means, but through chemical transmitters. Key central neurochemical systems such as the dopaminergic, serotonergic, and noradrenergic were linked to the speed of transmission across neural networks. Such psychological functions as psychomotor coordination, mood, and probably other behavioral factors were implicated in their functioning. It would be many years before it was established that these different neurotransmitter systems, of which there are many, differed in their associations with the regulation of the various behaviors. But following the discovery of the drugs it was clear that the state of depression, a composite of mood, behavioral, and cognitive elements, could be modulated, changed, and in certain cases, the disturbing elements neutralized entirely, by increasing the concentration of these neurotransmitters in the synapses. The process was not necessarily as simple as this. It may be, e.g., that other neurochemical events initiated by the enhanced transmission were responsible for the mood changes, but it had been clearly demonstrated that neurochemistry and psychological factors were seriously interrelated. This discovery and the postulating of specific hypotheses concerning the nature of the relationships of neurochemistry and the mental disorders set in motion a wave of research aimed at uncovering the nature of the links. The clinical studies, however, focused on links with a “diagnosis,” a disorder as a whole, and as previously noted, at the clinical level appeared to avoid the more difficult and more tedious attempts to uncover the relationships of the neurotransmitter systems and the specific behaviors and moods which make up the structure of the depressive and other related syndromes.

From a basic scientific viewpoint, the more logical approach to determining the links between neurochemistry and behavior would be to measure relationships

between specific neurotransmitter factors, for example, the concentration of serotonin in the central nervous system and a behavioral or psychological element such as psychomotor speed or the mood states of anxiety or anger. It was, in other words, necessary to work out the basic elemental relations between these two diverse areas of functioning before introducing into these studies, such entities on the behavioral side of the equation, as a complex mental disorder. Maas and I came to this conclusion based on our experience in the psychobiology of depression collaborative program [4]. We believed that the practice of using the diagnostic entity to represent the behavioral side of the neurochemical-behavioral equation, that is, in the attempt to uncover the specific chemistry associated with a “whole” disorder, was misguided. It was a common mistake in the overall clinical research effort to determine the “biological markers” of depression. Three decades later and following literally hundreds of studies, these biological markers, as noted, have not yet been found nor have we learned very much more about the neurobehavioral nature of depression.

In our work in the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression (CDS) (1980), we did, following the approach used in preclinical studies of the antidepressant drugs’ behavioral actions, attempt to identify the mood, behavioral, cognitive, and somatic factors that comprise the psychological side of the depressive disorder and then set out to devise methods for measuring the psychological facets as separate elements. This was in accord with the research approach followed by basic investigators aimed at identifying the specific behavioral actions associated with the various neurotransmitter systems, i.e., the behavioral actions in humans and animals produced by drugs whose specific neurochemical actions were to enhance or to interfere with the functioning of these systems. In this report, it is useful to note that such work is aimed at increasing knowledge of how the central nervous system regulates behavior and emotion, but that it also provides a basis for developing drugs which are more effective or act more rapidly than the ones currently available. What has already been learned about specific neurochemical-behavioral relationships is highly complex, but some of the findings in this area of basic research are important as background for understanding the unusual actions of the established antidepressants. The conclusions in this sphere are drawn mostly from a recent review paper by Morilak and Frazer [5] in which they summarize findings on associated behavioral factors, linkages relevant to three of the neurotransmitter systems most affected by the antidepressants, and, therefore, the systems whose levels of functioning are most likely to influence the state or define depression.

Neurotransmitter-Behavioral Relationships

From that paper, we learn that “a prominent role for serotonin in the brain appears to be to bias the behavioral repertoire of an organism away from a pattern of activation responses, and to promote a pattern of impulse control and behavioral

constraint.” Therefore, enhancing such a role could be easily seen to result in suppressing certain symptoms of negative emotion [6, 7] Serotonin increase will diminish impulsivity, aggression, or even suicidal ideation. Serotonin has also, long been hypothesized to play a role in anxiety and emotional reactivity, although sometimes in a contradictory manner, but apparently, always toward a pattern of impulse control during periods of higher arousal and locomotive activity. Contrarily, tonic elevation of extra cellular norepinephrine levels should produce changes in baseline behavioral activity indicative of an elevation in arousal, alertness, attention, or vigilance. Norepinephrine, therefore, appears more closely associated with the overall state of “behavioral arousal,” including effects on locomotion, eye movements, brain (electroencephalographic) activity, heart rate, and overt behavioral activity. Both human and animal studies find norepinephrine transmission associated with increases in behavioral and physiological indices of arousal, overactivity, and motility, while the decrease in level of norepinephrine is associated with sedation and behavioral inactivity. Animal studies tested these ideas in situations in which the mobility and the capacity of the animal in struggling, for example, in “swimming tests” [8] are measured. The studies demonstrate a relationship of these activities to the norepinephrine level. Both norepinephrine and dopamine increases appear to have a positive effect on the movement state, promote attention and arousal, facilitate interaction, and enhance motivation in reward activity situations to promote a subjective feeling of pleasure.

It has to be understood that the results of basic research on the behavioral associations of the serotonin system are sometimes contradictory, and that the knowledge that these neurotransmitter systems, serotonergic, noradrenergic, and dopaminergic, do not operate in isolation but interact in their functioning, make it difficult to provide clear demarcation of these behavioral associations. Yet it is hypothesized, we believe on a sound basis, that enhancing the functioning of the serotonergic system moves behavior away from activation and promotes a pattern of impulse control and behavioral constraint. Other research links it to the modulation of anxiety and aggressive impulses, aspects of mood that figure highly in the state of depression. On the contrary, increasing norepinephrine that is directly related to behavioral arousal, promotes motor activity, reduces immobility, and enhances alert and vigilant behavior.

When we think of how the depressive state is constituted, we are aware that anxiety, motor functioning, and cognitive clarity play focal roles in the state, and that certain theories (e.g., Abraham [9]; Freud [10]) saw a large role for feelings of hostility and repressed anger. It appears on the surface then that it might be simple to account for the therapeutic effects of the drugs by linking these AD drug- induced actions on the neurotransmitter systems to the changes in these elements of psychological function. We noted in the Collaborative Studies, e.g., that the initial behavioral changes included the reduction of anxiety that would be shown later, to be significantly associated with the drug-induced marked decrease in the concentration of the serotonin metabolite, 5-HIAA in the cerebrospinal fluid [11]. These neurotransmitter systems, however, are likely to be more complicated

in their interactions, and in their subsequent actions on behavior, so that we still do not have closure in achieving complete understanding of the basic therapeutic mechanisms. Nevertheless, it is important to have this knowledge of their associations with specific mood and behavioral states as background when we approach an analysis of the components of behavior that comprise the depressive disorder. The questions to be raised are whether now knowing that neurochemical systems are associated with the regulation of certain behavioral states, and that the drugs can be used to alter these relationships, are we not in a better position to expand our current understanding of the neurobehavioral structure of depression and the ways in which the disorder can be treated?

The drugs when used in this manner, were employed as “experimental tools” to test hypotheses relative to the enhancement or normalizing of these systems, issues of the roles of central neurotransmitter systems in creating or regulating the disorder. Drugs can be used to manipulate these systems in the service of advancing our knowledge in these respects, and thus, to facilitate the development of new, more effective drugs.

To fully unravel the neurobehavioral relationships that underlie the depressive disorders, we must first dissect, identify the various behavioral components and mood components, and uncover the basic dimensions underlying the disorder so that we can re-examine our current knowledge about the psychological structure of depression.

References and Notes

1. In critiquing the manner in which clinical trials of new antidepressants are currently conducted, I identified these research models as “diagnosis-specific” and “component-specific” (Katz, M.M., Bowden, C.L., Frazer, A. (2010). Rethinking depression and the actions of antidepressants: uncovering the links between the neural and behavioral elements. *Journal of Affective Disorders* 20:6–23.) The two models were compared detailing the limitations of the former in providing critical information on the new drug’s profile of action, i.e., the nature, timing and sequence of behavioral actions that it induces in the depressed patient. The almost exclusive use of the diagnosis-specific model for clinical trials is why it has taken so many years to accumulate the critical profile information on specific clinical actions, even for the long-established antidepressants. This issue is discussed in more detail in a later chapter.
2. Katz, M. M., & Maas, J. W. (1994). Psychopharmacology and the etiology of psychopathological states: Are we looking in the right way? *Neuropsychopharmacology*, 10, 139–144.
3. To investigate the role of biological factors in the causes or nature of depression, diagnosed patients are selected for a given study in accord with the DSM criteria. Therefore, whether a biological factor is specifically associated with depression is determined by comparing the presence and intensity of that factor in the depressed group with the degree of that factor as measured in another diagnostic group, e.g., anxiety disorders. Use of the diagnosis to characterize the overall clinical state of the patient bypasses, in effect, the need to delineate the behavioral, cognitive and affective components that comprise the disorder. Instead, the components are encapsulated in the diagnosis. By so doing any relationships that may exist between the biological factor and any of the behavioral elements of the disorder are obscured, making it more difficult to uncover them and limiting the amount of new information that any new study can provide.

4. Maas, J. W., et al. (1980). Biological component of the NIMH clinical research branch collaborative program on the psychobiology of depression, I: background and theoretical considerations. *Psychological Medicine*, 10, 759–776.
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8. Lucki, I. (1997). The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. *Behavioural Pharmacology*, 6–7, 523–532.
9. Abraham, K. (1911). Notes on the psychoanalytical investigation and treatment of manic-depressive insanity and allied conditions. In E. Jones (Ed.), *Selected papers in psychoanalysis*. London: Hogarth Press.
10. Freud, S. (1934). Mourning and melancholia. In S. Rado (Ed.), *Collected papers* (4th ed.). London: Hogarth Press.
11. Katz, M. M., Maas, J. W., Frazer, A., Koslow, S. H., Bowden, C. L., Berman, N., Swann, A. C., Stokes, P. E. (1984). Drug-induced actions on brain neurotransmitters systems and change in the behaviors and emotions of depressed patients. *Neuropsychopharmacology*, 11, 89–100.

Depression and Drugs

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