Has psychopharmacology entered a blind alley?

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W hile musing about “no really new medications are available or on the horizon,” some of my colleagues and friends keep asking if psychopharmacology has hit a blind alley and if we can expect any breakthroughs like those that occurred during the Golden Age of psychopharmacology in the mid-20th century. Those questions reminded me of an excellent commentary by Donald Klein published in 2008.1

Klein1 noted that between the 1950s and 1970s, “Therapeutic discoveries resulted from chance observations of unexpected clinical benefits or as inadvertent outcomes of blind pharmaceutical searches. The pace of discovery of entirely new classes of psychotropic drugs in the 1950s and 1960s was dizzying, and included lithium, lysergic acid diethylamide, chlorpromazine, iproniazid, reserpine, imipramine, chlordiazepoxide, haloperidol, and clozapine.” The earlier discovery of meprobamate was similarly serendipitous, as was the discovery of sildenafil for erectile dysfunction decades later. Because we have not seen a major discovery like these and many drugs we use are “me-too drugs” or modifications of existing drugs, Klein1 asked what stymied such generative serendipity over the next 40—now 50—years? He suggested several anti-serendipity factors: the expectation that serendipity would be replaced by rational drug design fostered by translational research; the radical compression of clinical time because of cost-control measures; and, ironically, the adoption of parallel-group, placebo-controlled, double-blind trials as the sole method for demonstrating drug efficacy. He noted that many discoveries were verified in chronic state institutions, where there was not much constriction of time for informed clinical observation of unexpected medication benefits as well as their follow-up. Klein furthermore noted the effect of the 1962 Kefauver-Harris FDA Amendments, which required “demonstration of acute medication efficacy before marketing, without any stipulation concerning effect size, translation into clinical benefit, determination of just who would benefit, systematic attention to long-term benefit maintenance,
or late-onset toxicities. The pursuit of short-term statistical superiority to placebo become industry’s Holy Grail of marketability. The fact that the National Institute of Mental Health abandoned funding the search for new medications and left the development to the pharmaceutical industry has further contributed to the decline of new drug discoveries.

Peter Kramer similarly emphasized the importance of careful long-term clinical observation in his description of Roland Kuhn’s discoveries of the effects of imipramine and of the concept of antidepressant as a new class of medications. Kuhn was able to test the effects of imipramine for 18 months and in patients who previously had not been taking any medication! As Kramer noted, moments of discoveries such as this can arrive only once: “Today, trials of new drugs attract people who have failed on available medications or people outside the medical system, not diagnosed in the ordinary course of practice—an unrepresentative sample.” Even substances of abuse (eg, the Cannabis study by Cohen3) and their clinical effects were studied in long-term observational studies that are no longer possible.

I am not discounting the psychopharmacology developments over the last few decades, but we have to ask how much of it has been really just “polishing” of old discoveries by developing “me-too drugs” or making more or less trivial changes to existing medications. Let’s face it, we have not developed any medications beyond the classes of drugs developed several decades ago. Renaming and reclassifying is not going to change anything. Nor have we been able to develop specific medications for certain diagnostic categories (eg, eating disorders). Many of our medications are quite nonspecific, used across various diagnostic categories. The Golden Age of psychopharmacology discoveries is long gone. Can we expect another one, or has psychopharmacology hit a blind alley? Can serendipity be revitalized as Klein asked? Probably not, because it also would require reversing the constriction of clinical discovery time and other profound changes. Klein1 offered a partial solution of implementing so-called “intensive design,” which is “repeated periods of intervention and nonintervention, judging whether benefit synchronizes with intervention.” Further changes may include long-term placebo trials beyond the usual 6 to 8 weeks—and possibly in the inpatient setting—or intensive trials with some non-psychiatric medications already on the market. Many have suggested including various objective measures, such as imaging, genetics, neuropsychologic testing, and psychophysiology, into development and trials of possible new medications. A new classification—Research Domain Criteria—based on mechanisms rather than symptoms has been created as a response to the less-than-ideal DSM classification. This classification is intended to guide us to develop a better understanding of the true biology of mental disorders, and therefore to develop better treatments. However, some doubt its proclaimed superiority because “it lacks the very scientific foundation it proclaims... and ignores the key clinical reality of sickness vs. wellness.” Others have proposed (and used) substances with high potential of abuse (eg, ketamine) or extraction of some components of drugs of abuse (eg, cannabidiol from Cannabis) for treating various mental disorders. But are those solid answers to our problems or yet another sign of a blind alley?

Psychopharmacology is treading water—an expensive one, considering what society pays to the pharmaceutical industry for “me-too drugs,” modification of old drugs, and now even for generic medications—past the intersection where it entered a long blind alley. Can we paddle back to that point? I don’t have a good answer, but we all need one.

REFERENCES