From too much and too little towards stratified psychiatry and pathophysiology

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As J. Rapoport points out in her incisive commentary, pediatric psychopharmacology stands now at the crossroads of both too much and too little. Certainly, the number of options now available to clinicians far exceeds the resources physicians could draw on even two decades ago. However, appreciation of this apparent cornucopia is tempered by awareness of how limited therapeutic benefits tend to be when examined in controlled studies and by increasing insight into the numerous secondary adverse effects that inevitably accrue. Too little benefit, too many adverse effects.

Rapoport eloquently echoes the observation that all of our present psychopharmacological options emerged as a result of serendipity based on conditions that no longer exist – chiefly the ability to carefully observe patient responses to systematic treatment trials during long-term inpatient hospitalizations (1). To advance the field, she urges us to seek ways of recapturing opportunities that may once again lead to fortuitous discovery. One benefit of the extension of health care benefits in the United States, dubbed “Obamacare”, is the requirement for the universal adoption of electronic medical records. Such systems could provide the basis for “psychopharmacological epidemiology” in what is arguably the most adventuresome health care system in the industrialized world. Heretofore, much of the clinical experimentation conducted under conditions of apparent necessity has been inaccessible to investigators. Adoption of harmonized medical record systems that can be searchable, while protecting patient privacy and confidentiality, could provide the essential infrastructure for recapturing serendipity (1).

However, simply trolling large data sets is unlikely to yield much clinical bounty. The needle of occasional therapeutic benefit is too slender to detect within the haystack of clinical complexity and the Tower of Babel of existing clinical records. As Rapoport notes, the optimism regarding repurposing older medications for psychiatric disorders has not been matched by much evidence of success to date. The answer, we hope, lies in shifting from the illusory distant goal of “personalized medicine” to the more modest and attainable one of “stratified psychiatry”, as recently advocated in the context of developing clinical tests (2). As shown by the example of human epidermal growth factor subtype 2 (HER2) in breast, ovarian, endometrial, non-small-cell lung and even gastric cancer (2), identification of effective means of stratifying on the basis of prognosis can lead to the development of effective novel therapeutic agents, in that case, the monoclonal antibody trastuzumab, also known as Herceptin.

So, what lessons can we glean from the molecular therapeutic advances being attained in oncology? Chiefly, that we must reinvigorate our efforts to understand pathophysiology. As psychiatrists cannot access brain tissue with the same facility as oncologists probe tumor samples, we will need to further develop indirect methods, such as those based on human induced pluripotent stem cells, as noted by Rapoport in her conclusion. Regardless of the method, the overarching goal needs to be to understand physiology, and the many ways it goes awry in pathophysiology. We must think in terms of systems, networks, and above all, functions. Fortunately, many of the elements and components required to carry out this endeavor are close at hand. Human brain function is increasingly being appreciated in terms of large-scale neural systems, i.e., spatially defined networks, which capture and condense complexity

which would otherwise remain unimaginable (3–5).

In the dazzling field of molecular genetics, simplistic notions that common variants would account for much of the substantial heritability of psychiatric disorders have been replaced by a focus on biological pathways and their underlying genetic networks (6). Genetic markers are no longer sought as sufficient clues to pathogenesis, but rather as indicators of the relevant physiological processes which can become targets for intervention. An illustration of our near-term objective was provided two decades ago by D. Klein in his seminal consideration of “false suffocation alarms, spontaneous panics, and related conditions” (7). Klein arrayed myriad clinical and laboratory observations in light of an evolutionarily motivated theory of the etiology of panic disorder, i.e., that spontaneous panic attacks result from dysfunction of an inborn suffocation alarm system. This formulation made sense of seemingly inconsistent observations and has motivated hundreds of subsequent reports, many of them relevant to anxiety disorders in children and adolescents. However, the greater lesson is encoded in the conclusion, which would be well adopted in pediatric psychopharmacology and clinical neuroscience: “The history of medicine amply demonstrates the value of the splitting diagnostic approach as well as the dangers of hardening of the categories. An active experimental, therapeutic, and physiologic challenge approach to psychopathology may move us from symptoms to a grasp of deranged circuitry” (7).

References

1. Klein DF. The loss of serendipity in psychopharmacology. *JAMA* 2008;299:1063-5.
2. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry

to develop clinical tests and what to do about it? *Mol Psychiatry* 2012;17:1174-9.

3. Smith SM, Fox PT, Miller KL et al. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci USA* 2009;106:13040-5.

4. Yeo BT, Krienen FM, Sepulcre J et al. The organization of the human cerebral

cortex estimated by functional connectivity. *J Neurophysiol* 2011;106:1125-65.

5. Cortese S, Kelly C, Chabernaud C et al. Towards systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *Am J Psychiatry* 2012;169:1038-55.

6. State MW, Sestan N. Neuroscience. The emerging biology of autism spectrum disorders. *Science* 2012;337:1301-3.

7. Klein DF. False suffocation alarms, spontaneous panics, and related conditions. An integrative hypothesis. *Arch Gen Psychiatry* 1993;50:306-17.

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A European perspective on paedo-psychiatric pharmacoepidemiology

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J. Rapoport's paper confronts the reader with the central statement that in the recent past some over-acceptance of drug treatment for children and adolescents with mental disorders has emerged, contributing to the development of a reductionist psychobiology. This may be regarded as a major current threat to the identity of child and adolescent psychiatry. The present commentary concentrates on findings indicating that this over-prescribing of psychotropic medications in children and adolescents differs in magnitude in the various countries. More detailed analyses are needed for a better understanding of these differences.

International studies have shown that the prescription rates of psychotropic medications in children and adolescents vary substantially across countries. The prevalence of any prescription of psychotropic drugs in youth in the year 2000 was substantially greater in the US (67 per 1,000 people) than in the Netherlands (29 per 1,000) and in Germany (20 per 1,000) (1). Marked differences among countries have been observed also for individual groups of drugs. For instance, the utilization of antidepressants in 0–19 year olds in the year 2000 in an US dataset (16.3 per

1,000) largely exceeded that of three Western European countries (1.1–5.4 per 1,000) (2).

There have been also changes over time in both the total number of prescriptions and the utilization of the various drugs. The number of all psychotropic prescriptions for children has risen between the years 2000 and 2002 in Europe, South America, and North America (3). In the Netherlands, the prescription rate of all antipsychotics, benzodiazepines, antidepressants, and psychostimulants increased from 11.1 per 1,000 in 1995 to 22.9 per 1,000 in 2001 (4). These time trends have been also observed for individual groups of drugs, including stimulants, the most widely prescribed psychotropics in children and adolescents, but also antidepressants and antipsychotics.

However, most of the data on time trends are biased by the unrepresentativeness of the study populations and the short and rather accidental observation periods. The long-standing tradition and quality of Scandinavian registers, including data on prescriptions, allow studies which are not affected by these biases. Our own recent study (5) based on the Danish register, analyzing all dispensed prescriptions in the population aged 0–17 years between the years 1996 and 2010, allowed a consistent analysis of patterns of psychotropic medication over fifteen consecutive years. The major findings were the following. First, the prevalence of all dispensed psychotropic medications over these fifteen years showed a nine-fold increase. This increase was much re-

duced after adjustment for the increasing number of patients seeking help from public health services. However, even after adjustment, there was still a two-fold higher rate of dispensed prescriptions over the observation period. Secondly, this trend was most pronounced for stimulants, with a twenty-three-fold increase in non-adjusted prevalence rates and a still eight-fold increase in adjusted prevalence rates. For antidepressants, there was a 9.5-fold increase (1.8-fold increase after adjustment). For antipsychotics, there was a 6.6-fold increase (two-fold increase after adjustment). Despite increasing numbers, these Danish rates were lower than in many other European countries and particularly in the US.

Vitiello (6) suggested that many factors affect prescription of medications in children, including variations in health service organization, differences in diagnostic systems, adherence to clinical practice guidelines, drug regulations, availability and allocation of financial resources, and cultural attitudes towards child and adolescent mental disorders. It remains unclear whether the Danish public health system counteracts to some extent the impact of market forces on prescriptions. However, given the similar organization of health services in Scandinavian countries and some indication of markedly different prescription rates for psychotropic medications in these countries (7), there is not much room for the argument that public health services *per se* unfold strong control of market processes through strict drug