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Review article

Ethical challenges in developing drugs for psychiatric disorders

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ABSTRACT

As the classification of mental disorders advances towards a disease model as promoted by the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC), there is hope that a more thorough neurobiological understanding of mental illness may allow clinicians and researchers to determine treatment efficacy with less diagnostic variability. This paradigm shift has presented a variety of ethical issues to be considered in the development of psychiatric drugs. These challenges are not limited to informed consent practices, industry funding, and placebo use. The consideration for alternative research models and quality of research design also present ethical challenges in the development of psychiatric drugs. The imperatives to create valid and sound research that justify the human time, cost, risk and use of limited resources must also be considered. Clinical innovation, and consideration for special populations are also important aspects to take into account. Based on the breadth of these ethical concerns, it is particularly important that scientific questions regarding the development of psychiatric drugs be answered collaboratively by a variety of stakeholders. As the field expands, new ethical considerations will be raised with increased focus on genetic markers, personalized medicine, patient-centered outcomes research, and tension over funding. We suggest that innovation in trial design is necessary to better reflect practices in clinical settings and that there must be an emphasized focus on expanding the transparency of consent processes, regard for suicidality, and care in working with special populations to support the goal of developing sound psychiatric drug therapies.

Contents

Abbreviations: FDA, Food & Drug Administration; NIH, National Institutes of Health; NIMH, National Institute of Mental Health; RCT, randomized controlled trial; RDoC, research domain criteria; RPCT, randomized placebo controlled trail.

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1. Introduction: a brief overview of ethical issues in clinical psychiatric research

The use of psychotropic medications to treat individuals with psychiatric disorders has become one of the mainstays of treatment in the modern era. The advent of pharmacological treatments in the discipline of psychiatry began in the late 1950's with the introduction of chlorpromazine, an antipsychotic medication. Since that time, there have been many phases in the development of pharmaceutical treatments for psychiatric disorders, which have clearly changed the scope and distribution of the fields of psychiatry and neurology. For example, vitamins and antibiotics allowed targeted treatment of psychosis, various dementias, and delirious states (e.g. pellagra, syphilitic encephalitis, cases of Wernicke-Korsakoff Syndrome and alcohol related amnestic disorders). Such treatments radically changed the course of previously incurable mental afflictions. In addition to their curative power, these treatments also provided insight into the pathophysiology of many mental disorders, greatly improving our understanding of these afflictions (Ban, 2001).

Serendipity, it is argued, has been a powerful source of psychopharmacological discoveries, with insights both in psychopathology and pharmacotherapy (e.g. the discovery of isoniazid's anti-depressive properties in patients with tuberculosis, chlorpromazine's shift from an anesthetic to an antipsychotic, and the depressive effects of reserpine in patients with hypertension; Klein, 2008). While this review is not aimed at providing a detailed history of the development or use of drugs in psychiatry and neurology, these examples show that early efforts at developing drugs targeting the central nervous system were focused on an increased understanding of complex conditions and the treatment of those conditions. To some extent, many scientific challenges about drug development in psychiatry have not changed much; it is obviously challenging to create a valid scientific hypothesis for disorders that are imperfectly understood from a pathophysiological perspective and classified in ways that are often debated if not polemic in the profession and in the population.

This state of affairs might change as mental disorders classification become closer to a disease model as promoted by the NIMH Research Domain Criteria (RDoC) (Casey et al., 2014; Cuthbert and Insel 2013; Morris and Cuthbert, 2012). The belief is that with better insight into the neurobiology behind the phenomenological manifestations, clinicians and researchers will be able to determine the efficacy of treatments with less diagnostic heterogeneity. But there are thoughtful observers who doubt that psychiatry has the ability to distill these experiences to a basic biological or physiological level to the extent that RDoC proposes (Frances, 2014). To be sure, this lack of pathophysiological understanding and diagnostic validity also becomes an ethical issue whenever patients/subjects and public resources are to be used to develop and test a drug for the condition in question. Are the science and knowledge worthwhile and valid? Are the risks justified by the quality and utility of the results expected to be gained from the research? Good science is certainly an ethical matter when research is to be conducted with limited resources and exposure to risks for participants. Despite the uncertainties of pathophysiology and etiology of psychiatric disorders, drug development in this field can be both ethical and scientifically productive. Clearly, many psychotic, anxious, depressive and manic individuals do fare better with medication than they would otherwise. And drug development can and does to some extent inform etiological understandings of mental conditions.

Many of the early attempts at studying psychoactive substances in the treatment of psychiatric illnesses could be deemed problematic were they to be presented to a research ethics committees in the present era (Miller, 2014). Were patients apt to give consent to their involvement in the research? Was there a valid scientific hypothesis or equipoise? What about blinding, randomization, independent review? Were the burdens of research fairly distributed? It seems quite clear that until the 1960s, many patient-subjects, in many settings, were actually deceived into being used for clinical research, including for drug development purposes, while they believed they were receiving individualized clinical care.

After the Second World War, many of the ethical challenges of medical research became more salient. The way psychiatry and medicine could be used by ideology and political power was exposed during the famous Nuremberg trial of physicians under the Nazi government (Lifton, 1986). There was considerable development of the way medical research was going to be performed after the exposition of those terrible abuses. The Nuremberg code particularly emphasized the importance of informed voluntary consent (Shuster, 1997). The Declaration of Helsinki was adopted in 1964 and became an international standard (World Medical Association, 2001). This was then followed by the Belmont report, which was presented in 1979 and proposed principles to which IRBs still refer today. Interestingly, but sadly, it is often the identification of terrible abuses, scandals or other ethical challenges that paved the way to significant reflections, regulations and policy statements that changed the way clinical research, including that of new drugs in psychiatry, was to be conducted.

The development of drugs in psychiatry remains ethically challenging for several reasons. As scholars have pointed out, many of those challenges are not unique to psychiatric research (Chodoff, 1999). Psychiatry as a field may be particularly susceptible to ethical criticism, and part of this may relate to high degree of stigma that has and continues to affect the entire discipline. Moreover, individuals suffering from mental disorders are perceived as being particularly vulnerable, and perhaps more so than individuals without such a diagnosis. Psychiatry and the patients seen by psychiatrists are somehow different than the rest of patients in medicine, or that is at least what pervades not only the public's perception but frequently health care professionals, *writ large*. The gravity of strong emotions and objections to psychiatry as a discipline have given rise to organized groups, such as the anti-psychiatry movement, which criticize and emphasize the discipline's value-laden history, focus on vulnerable populations, the nature of problematic behaviors, and the use of coercion at times. Prior analyses of this topic have been generally focused on human subject protections in the context of clinical trials and have called for a more evidence-based approach to human subject review processes (Frank et al., 2003). In this review, ethical challenges pertaining to clinical research and drug development generally will be presented in a broad perspective, but with specific attention to how ethical challenges manifest themselves in the context of the development of psychotropic drugs/drugs for psychiatric disorders.

In the current paradigm of bioethics and research ethics, justification for conducting a pharmacologic research investigation, must address a number of key items, including: (i) proving

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