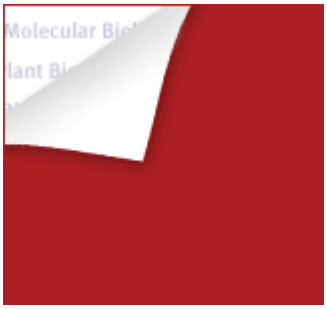
*Science* 19 July 1996:
Vol. 273. no. 5273, pp. 318 - 319
DOI: 10.1126/science.273.5273.318







POLICY FORUM

# Psychiatric Drug Development in Japan

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While psychiatrists in the West are reaping the benefits of the surge in drug development during the past 10 years, psychiatrists in Japan are currently treating mental illness with a psychopharmacologic armamentarium that was considered state of the art in the United States in the early 1980s. None of the new generation antidepressants, antianxiety agents, or antipsychotics that have made great changes in the way psychiatry is practiced in the West have yet been approved by the Japanese Ministry of Health and Welfare (MHW). Considering Japan's cutting edge position in most other areas of technology, this lag seems a bit surprising.

A closer look at the Japanese drug approval system and its relation to mental health makes some of the reasons for this lag clearer. First, even if a drug has been approved in the West, there is an incredible cost to the pharmaceutical industry in carrying out the clinical drug trials that need to be repeated in Japan. This financial investment may prove too burdensome for a drug company, especially if the market for the product seems sparse. Additionally, because of inherent difficulties in the way drug trials are carried out in Japan, the methodology often has flaws, and subtle psychopharmacologic drug effects may not be seen.

Prozac (fluoxetine, produced by Eli Lilly), which began to dominate the antidepressant market in the United States in the late 1980s, is not being developed in Japan. It is our understanding that this is because of the high cost of redoing the clinical drug trials and the perceived lack of an adequate market. Depressed individuals in Japan often do not visit their family physician, and if they do they are often told that they just need to relax more. The other selective serotonin reuptake inhibitors besides Prozac, including Zoloft (sertraline, Pfizer), Paxil (paroxetine, SmithKline Beecham), and Luvox (fluvoxamine, Solvay), have had ongoing drug trials in Japan since the early 1990s, although approval applications for these drugs have not yet been submitted to the MHW.

Flaws in drug trial methodology seem to have resulted in the inability of Buspar (buspirone, Bristol-Myers Squibb) to be approved. Buspar, a non-benzodiazepine anxiolytic that has been shown to be effective and has been available in a number of countries since the 1980s, was determined to be no more effective than placebo by two multicenter double-blind trials in Japan (1). However, close scrutiny of these studies shows that too few patients at too many centers led to intersite variation; in addition, although more severely anxious patients would be expected to respond, mildly anxious patients were included in a protocol that was not long enough to detect improvement in a medication with subtle anxiolytic effects (2). Similar protocol designs in Japan were not even sensitive enough to find benzodiazepines (that is, Valium) superior to placebo for anxiety in five of six multicenter placebo-controlled studies, even though studies performed outside Japan have concluded overwhelmingly that anxiolytics are more effective than placebo (2). Although psychotherapy is thought to be more pertinent for patients with low levels of anxiety, most Japanese psychiatrists do not think that buspirone has any utility and usually prescribe a benzodiazepine for patients with all degrees of anxiety.

One important antipsychotic drug introduced in the early 1990s in the West is Clozaril (clozapine, Sandoz). Although clozapine is virtually free from extrapyramidal motor side effects and has been shown to have enhanced efficacy in 30 to 40% of otherwise treatment-resistant schizophrenics (3), it is not yet approved in Japan and has not gained the favor of Japanese psychiatrists. Although a clinical trial is ongoing, a trial of clozapine in Japan in 1974 in which the mortality rate due to agranulocytosis was felt to be too high has left many Japanese psychiatrists with an understandable hesitancy toward its approval. There is also concern that frequent testing for lowered white blood cell counts—a known but uncommon side effect—makes patient quality of life unacceptable. Sandoz has minimized the risk of agranulocytosis in the United States by requiring that patients register in a nationwide blood testing data bank before they can receive the drug. In addition, prospective patients must have already failed a trial of two standard antipsychotics. The risk of agranulocytosis is greatest during the first 3 months of treatment;

the cumulative incidence is 0.8% after 1 year and 0.91% after 1.5 years (4). Clozapine is now widely used in the United States and other countries and is thought to be responsible for reduced symptom severity and decreased hospital stays. Japanese patients with chronic schizophrenia usually receive more than one antipsychotic at the same time, and many of them spend many years or their whole lives in for-profit private psychiatric hospitals.

Other novel psychiatric medications have been approved in the United States but not yet in Japan. These include the antidepressants Wellbutrin (bupropion, Glaxo Wellcome; U.S. approval in 1989, not in development in Japan), Effexor (venlafaxine, Wyeth-Ayerst; U.S. approval in 1994, currently in development in Japan), and Serzone (nefazodone, Bristol-Myers Squibb; U.S. approval in early 1995, currently in development in Japan), as well as the antipsychotic Risperdal (risperidone, Janssen; U.S. approval in 1994, with plans to enter the Japanese market in mid-1996) and a drug for alcohol dependency, REVIA (naltrexone, DuPont Pharma; U.S. approval in 1995, not in development in Japan).

Yutaka Mizushima, a past member of the MHW's New Drug Committee and currently an Upper House Parliament Councilor and member of the Committee on Health and Welfare, is trying to initiate changes in the system. He has noted that there are too many investigators at too many sites with too few cases at each site, and many of the investigators do not have sufficient knowledge or experience to perform drug trials (5). The Drug Approval Committee of the MHW has traditionally been composed of university professors, who serve on the committee in their spare time. Often, outcome end points have been unclear, and it is the doctors' subjective feelings about effectiveness rather than objective measures that have determined the outcome of trials. This process can lead to claims that ineffective drugs are effective, and vice versa (6).

Clinical drug trials cannot ascertain the degree of improvement in objective outcome measures (for example, quality of life, longevity) unless they are of adequate length and have adequate follow-up. This is not yet the case in Japan. After a drug has passed clinical trials, the MHW tends to approve the drug for a wide range of related conditions without assessing efficacy (7). Some foreign pharmaceutical executives have commented that it is often difficult to get the chief investigators (usually academic physicians) to exclude protocol violations or to discuss methodology with them. The general consensus is that the primary investigators have their own ways of doing things and do not like to hear what the drug companies have to say.

On top of these difficulties, the combination of the antiviral Sorivudine and the anti-cancer drug 5-fluorouracil was associated with 15 deaths in 1993; as a result, both the MHW and the drug companies have become especially sensitive to adverse effects, and the drug approval process has become

even slower. Although the MHW charged Nippon Shoji, the manufacturer of Sorivudine, with failure to report two of three deaths that occurred during phase III of the clinical trials and failure to provide adequate package warnings on this side effect, poor and hurried data review by an inadequately staffed drug approval committee at the MHW is thought to be the actual cause of the tragedy (7). In response, the MHW recently proposed a plan to take effect in 2 years that includes hiring a third-party medicinal review organization to monitor the clinical drug trials, increasing drug trial site inspections, and more closely reviewing informed consent procedures (8). There are also plans to greatly increase the size of the MHW staff; at present, considerably fewer personnel are involved in each new drug application than in Western countries, and many are not scientifically qualified (9).

At the end of 1995, at the Third International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (in Yokohama), the international community attempted to make the results of drug trials reciprocal between nations. This action placed additional pressure on Japan to improve its system. Reciprocity would greatly reduce the cost of drug development and would make the introduction of drugs to the Japanese market much more palatable for the international pharmaceutical companies. The establishment of an international organization that would review the clinical drug trials of a compound and make recommendations for expedited approval in other countries that agree to this protocol is one way to alleviate the need for repetitive studies. If such an organization were funded by the various drug approval agencies of the respective countries, the burdensome reevaluation costs incurred by each country could be considerably reduced. [This kind of process would need to take into consideration any ethnic differences in drug metabolism; for example, Asians seem to have lower hepatic metabolic capacities than do Caucasians, and this difference may lead to differences in dosage (10).]

The impetus for the MHW to improve its system has also come from sources other than the Sorivudine incident. Recently, the MHW reported that one of its departments did not adequately assess blood products used to treat hemophilia for the absence of the human immunodeficiency virus (HIV) in the mid-1980s, even though the U.S. Food and Drug Administration had issued a recall order for these products (11). Limitation of their import was delayed by many months, and it is now estimated that about 40% of Japanese hemophiliacs have acquired HIV from blood products (11).

Both the Sorivudine and blood product incidents have slowed drug approval in Japan by making the MHW more cautious. Methodology flaws inherent in the Japanese drug trial system will be difficult to eradicate, however, because of the strong line of authority from the primary investigator down to the pharmaceutical drug trial coordinator, which creates an impediment to educating the investigator about proper drug trial

methodology. In addition, because different investigators at different sites each have their own way of carrying out a study, the standardization of outcome measures for psychiatric disorders will be difficult as well. If Japan can agree on accepting more data from studies previously done in other countries, the drug approval process could proceed much more quickly, and more drug companies would submit approval applications if their costs dropped. Efforts to educate primary physicians and the general population about psychiatric illness would help to broaden the market for these treatments by decreasing stigma and increasing awareness about the large biologic component of many of these disorders and their cost to society.

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*Science*. ISSN 0036-8075 (print), 1095-9203 (online)