

# Antidepressant Drug Development in Japan:

## Current & Future Horizons

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**A**lmost ten years has passed since it was noted that the number of new psychiatric drugs on the market in Japan had significantly lagged behind Western countries.<sup>1</sup> How has this changed over the last ten years, and what are the current challenges for pharmaceutical companies trying to enter this potentially lucrative market, especially for the most widely-used class of psychotropics, antidepressants?

Although large epidemiological studies have not been done in Japan, it is thought that up to 6 million Japanese suffer from depression<sup>2</sup> with a lifetime prevalence of 13–17%.<sup>3</sup> This is similar to that seen in Western countries: the Depression Research in European Society (DEPRES) study found that almost 16% had suffered from depression in their lifetime.<sup>4</sup> A large proportion of depressed patients are undiagnosed or even untreated in milder forms of the disease and often have physical symptoms;<sup>5</sup> 75% of these patients are thought to be seen in the general medical clinics,<sup>6</sup> where it is estimated that the primary reason for up to 6% of all patients' visits to the clinic is depression.<sup>7</sup> Many psychiatrists promote themselves as practitioners of 'Psychosomatic Medicine' or 'Neurologic Internal Medicine', however, and these clinics would then be classified as 'Internal Medicine' or 'General Medical Clinics' for statistical purposes. The current antidepressant market size in Japan is equivalent to about US\$650 million, with sales of paroxetine (Seroxat/Paxil) making up approximately half of this value.

Clinical trials and many clinicians in Japan use the criteria published in "Diagnostic and Statistical Manual of Mental Disorders, 4th Edition"<sup>8</sup> (DSM-IV) to categorise their diagnoses. However, many psychiatrists still use traditional Japanese nomenclature of psychiatric illnesses, using terms like 'Autonomic Nervous

Dysfunction', 'Vague Somatic Complaints', 'Psychologic Reaction' to describe conditions that are probably largely comprised of depressive and anxiety disorders as defined by DSM-IV. This is partly due to cultural habit, partly due to lack of training in the use of DSM-IV criteria, and partly due to hesitancy on the part of the clinician to stigmatise the patient with a diagnosis of depression. This disparity of diagnosis can lead to difficulties when comparing cases with the international literature, and could lead to treatment options being missed.

### Regulatory effect on antidepressant trials in Japan

While the market has seen the entry of the SSRIs fluvoxamine ('Luvox' from Fujisawa, and 'Depromel' from Meiji Seika), paroxetine ('Paxil' from GSK), and the SNRI milnacipran ('Toledomin' from Asahi Kasei-Janssen), other blockbuster antidepressants including sertraline ('Zoloff' from Pfizer), fluoxetine ('Prozac' from Eli Lilly) and others are either still in development or have essentially been abandoned with respect to the Japanese market.

Slowly, the Japanese regulatory system run by the Ministry of Health Labor and Welfare (MHLW) has required that the criteria for clinical development in Japan catch up with the quality seen in the West. For example, none of the antidepressants on the market in Japan has been studied using placebo controls in Japan, but this is now changing. Previous clinical developments have pitted the new drug against a drug already on the market using a 'non-inferiority' method of comparison. In studies of antidepressants, this method is known to be susceptible to 'placebo effects', ie, depressive symptoms lifting due to effects other than pharmacologic drug effect. For example, if patients know that they are definitely receiving an 'active' drug, having been told that

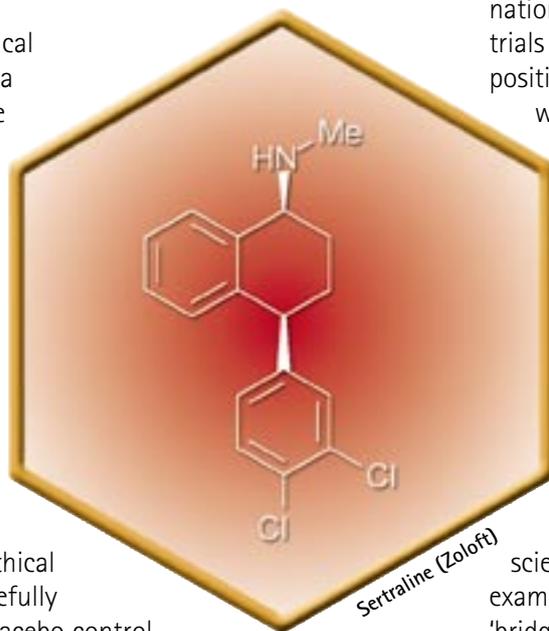


there is no placebo arm in the study, this could be sufficient to cause a response. Additionally, some study subjects with relatively mild depression might be likely to recover naturally over time, whichever treatment they receive.

Traditionally, conducting clinical trials in depression has been a sensitive topic because of the perceived risk of suicide in an untreated depressed patient. However, some Japanese investigators have been calling for a number of years for use of placebo in carefully selected depressed patients. Recent surveys have found that the majority of Japanese psychiatrists think that, at least in principal, it is both ethical and scientifically valid to carefully conduct clinical trials with placebo control in depressed patients in Japan. This has been backed by a push from industry, presenting data from studies conducted in the West showing that the suicide attempt rate is no different in active vs. placebo arms. The Japanese regulatory authorities have recently requested that compounds starting clinical development in Japan should have dose-finding studies conducted against placebo.

Other compounds have already completed clinical studies in Japan using a 'pseudo-placebo' (ie, very low doses of an active comparator), or relapse prevention studies (in which some subjects who respond to the active drug are then switched to placebo and compared against those remaining on the active drug). Companies developing these drugs are now being told to conduct a formal dose-response study with placebo control before submitting a New Drug Application (NDA) for sale in Japan. Naturally, this has delayed the entry of these antidepressants into the market in Japan by many years and cost many more millions of dollars in R&D expenditure.

The effect of the political climate on drug development in Japan also cannot be underestimated. The authorities running the Japanese national medical insurance system appear very careful to contain a potentially explosive market for such drugs as antidepressants, which could conceivably be used for persons spanning a wide range of psychological distress. In the late 1990s,



virtually the entire class of 'cerebral metabolic enhancers' used for post-stroke syndromes and other cognitive disorders including depression was eliminated from the marketplace because of perceived lack of efficacy and high cost to the national health system. Several post-marketing trials were requested and the resultant lack of positive findings led to the decline of a market worth hundreds of millions of dollars.

### Bridging of global data into Japan

Adoption of the ICH guidelines<sup>9</sup> in Japan makes it possible in principal to 'bridge' clinical trial data from outside Japan into the Japanese data package for NDA. However, whether this is permitted in practice for a given drug could be considered to depend more on the potential importance of that drug to medical care in Japan, than the scientific logic of the data to be bridged. For example, a novel drug for influenza was able to 'bridge' overseas data to meet a considerable portion of the Japanese requirements and gain entry into the Japanese market. Conversely, antidepressant drugs used in millions of patients over several years in multiple countries outside Japan are still required to have pharmacokinetic,

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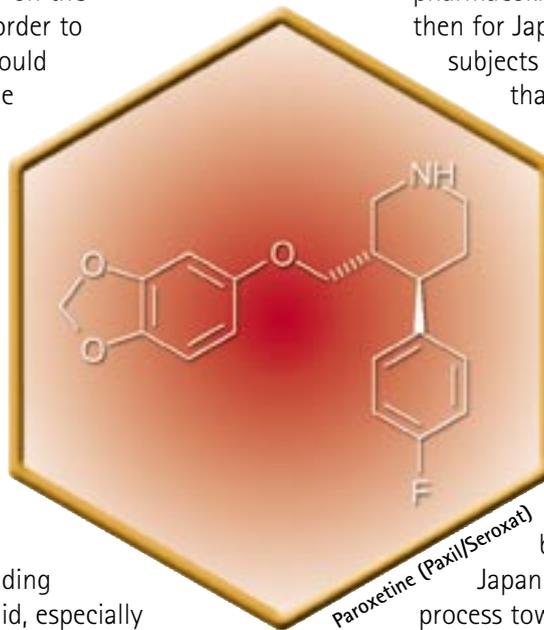
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dose-finding, elderly, and long-term studies conducted within Japan. In addition, a non-inferiority trial comparing the developmental drug with an antidepressant already on the market in Japan is also required in order to determine how the drug's action should be viewed *vis a vis* prior drugs on the Japanese market and in a Japanese medical environment.

We would hope that, eventually, antidepressants could be approved in Japan with bridging studies. For example, if a direct comparison between Japanese and Western persons in a Phase I study finds similar pharmacokinetics, and if a dose-finding study in Japan shows similar dosing and similar safety and tolerability with global dose-finding studies, then a NDA would seem valid, especially for a drug that is already on the market internationally. Further comparison with a drug already on the Japanese market in a non-inferiority study where both groups show equal likelihood to respond does not seem to add substantial clinical information to the approval



process of this drug in Japan. In addition, if a direct comparison of Japanese to Western persons in a Phase I study finds similarity in pharmacokinetics, it might even be reasonable then for Japanese study sites to contribute subjects to a global development program that would also lead to a NDA in Japan, just as centres across continents now participate in multinational clinical trials leading to NDAs in the USA and Europe.

### Conclusion

The factors confronting the clinical development of antidepressants in Japan are also common to other CNS medicinals in Japan. Both scientific logic and political mechanisms from both within as well as from outside Japan might be able to nudge the approval process towards accepting more bridging studies, as well as global studies done with contributing Japanese sites for NDA in Japan.

Western companies hoping to enter the CNS market in Japan should consider partnering with a company already experienced in the

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development of CNS compounds in Japan in order to avoid the pitfalls of delayed timelines and even requirements to repeat studies. As in many areas of doing business in Japan, one needs to have access to Japanese experience, and the will to persevere and to dig deep into one's pocket before hoping to succeed in the land of the rising sun.

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