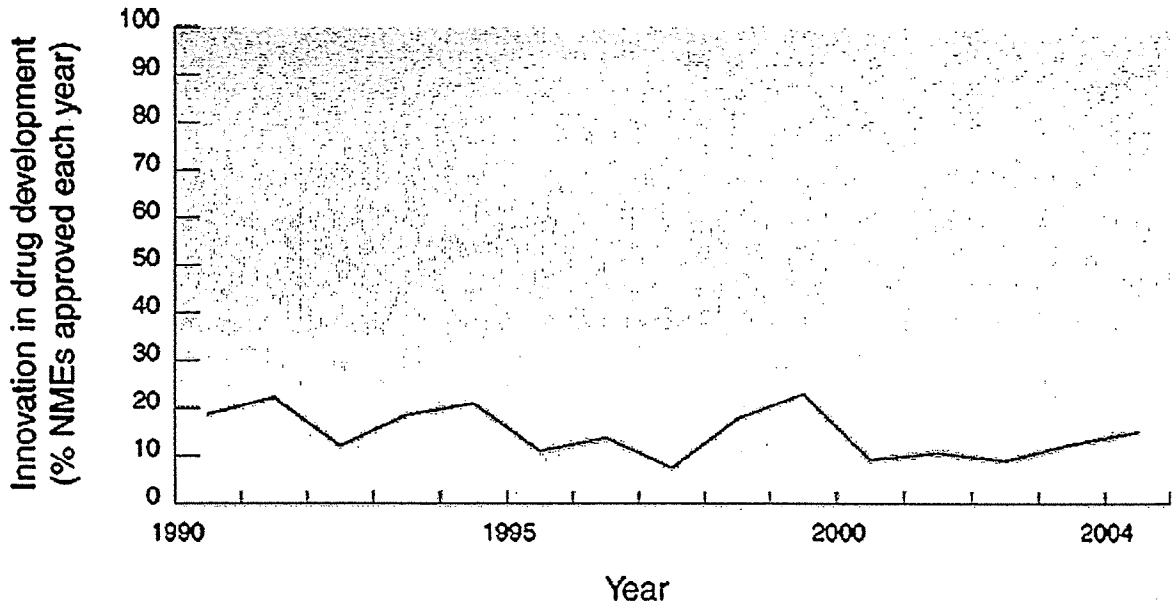

Figure 1 New drug applications (NDAs) approved in calendar years 1990–2004 by the US Food and Drug Administration (FDA) and the new molecular entities (NMEs) subjected to priority regulatory review while offering a significant improvement compared with marketed products in the treatment, diagnosis, or prevention of a disease. Innovation in drug development, as defined by the percentage of these breakthrough NMEs in relation to all NDAs approved in each calendar year, remained low for more than a decade. This further underscores the importance of recognizing (1) pharmacology and pharmacogenomics as experimental lines of scientific inquiry and (2) the attendant ethical obligation to prospectively pursue pharmacogenomics-guided drug development models (instead of the traditional 'wait-and-see' approach) that can improve innovation rates in drug development. Reproduced with permission from Ozdemir V.[15] 2

CEOs left office in 2004, a 300% increase in CEO departures since 1995.[38] Within the health care sector in 2004, CEO dismissals rose to 16.2%.[38] Nearly a third of all CEO resignations in 2004 were related to failure to meet demands for financial returns by increasingly impatient shareholders. Notably, the CEOs removed for inadequate performance had a median tenure of 5.2 years in the United States; in Europe, the situation was more difficult, with poorly performing CEOs remaining only for a median of 2.5 years. According to Lucier and colleagues, corporations "have reached a tipping point, in which power in the corporation is permanently shifting away from chief executives." In this climate of risk-averse and demanding shareholders and CEOs increasingly anxious about maximizing returns on a quarter-by-quarter basis, new pharmacogenomic technologies are being implemented.[39,40] Thus, it is difficult to reconcile the short-lived (2.5–5.2 years) tenure of the CEOs with new health technologies (eg, -omics biomarker platforms) that require long-term investment before tangible financial returns can be observed.

What incentives, then, can be put in place for corporate directors (as well as shareholders) to voluntarily exhibit socially responsible commitments to genomic technologies to achieve targeted therapeutics that, while potentially reducing short-term revenues,[34] may increase long-term retention of products (ie, safe and effective drugs) in the market? In the case of new genomic technologies, important social structural aspects,[15,32,33,38–40] such as those discussed above (eg, increased executive turnover and shareholder demands in favor of expediency), that can impact commercial or academic pharmacogenomic research and professional conduct may be dismissed or mistakenly ignored in the framing and future projections of these technologies.[41,42] To this end, a multidisciplinary learned society, such as the American Federation for Medical Research (AFMR), would be uniquely positioned to play a pivotal leadership role in facilitating dialogue across different professional languages and norms at the intersections of social sciences, research governance in public and private sectors, and professional practice of clinical

pharmacology and human genetics research to best realize the dream of pharmacogenomics-guided personalized medicines.

Regardless of the various sociologic, technology-based, or commercial factors and motivations that impede or facilitate the development of pharmacogenomic tests at the point of care, the fact is that the traditional model of drug development, with its focus on finding 'the next blockbuster drug,' is increasingly viewed as no longer realistic or viable.[37] Often overlooked is the fact that most recent blockbuster drugs were likely the 'lower-hanging fruits' resulting from rational and scientific drug development in the second half of the twentieth century. Further, many blockbuster drugs initially developed for broad use in the population have, on prescription in larger patient samples, been withdrawn from the market because of serious toxicity, a lack of effectiveness, or adverse drug-drug interactions. In effect, drug development without accompanying clinical biomarkers to customize prescriptions amounts to a statistical time bomb: when drug exposure exceeds the 1,000 to 3,000 patients collectively enrolled in typical premarketing clinical trials, members of the broader patient population who do not reflect the 'average' biologic or demographic attributes of trial participants are invariably exposed, leading to adverse drug-related events.

Exposing patients in clinical trials or during the postmarketing phase to partially preventable risks becomes a more acute and palpable social and ethical concern, especially when we consider that pharmacology is an experimental science amenable to proactive and prospective biomarker applications long before drug-related problems emerge. We submit that it is essential for both drug developers and regulators to adopt a longer-term vision that projects beyond the immediate goal of obtaining regulatory approval toward an enhancement of the entire life cycle and quality of a medicinal product. That is, prompt and timely introduction of new drugs to patients should be balanced against their sustainable use in the clinic, without postregistration withdrawal.[43]

Introducing noncustomized drugs in the clinic does not, in the long run, benefit many of the key actors in knowledge-based economies, whether they are patients or industry shareholders. Any costs incurred for postmarketing safety monitoring of drugs, such as frequent liver or kidney function tests, are ultimately transferred from the drug manufacturer to the patients and the payors.[44] Looking through the lens of global public health,[45] unfavorable perceptions about the societal commitment of a drug manufacturer on a given product withdrawn from the clinic will also have multiple detrimental effects on other compounds in their drug development pipeline: employee morale may suffer, thereby seriously undermining corporate initiatives to develop an equitable and attractive workplace environment that will retain highly trained and costly staff, whereas the broader mission of creating public benefit and ultimately safeguarding corporate and fiduciary responsibilities toward shareholders will be jeopardized.[46–48]

Future Outlook

As noted by David and Foray, commenting on the evolution of knowledge-based economies and civil societies, "[d]iscoveries in many domains are...made in the course of unplanned journeys through information space."[49] The genealogy of scientific progress can be even more complex in the case of interdisciplinary dialogues and experiments. Simply 'chunking' pharmacogenomics and human genetics together in conceptual proximity as two identical disciplines would be inadequate for a balanced reconciliation of their nuanced differences in science policy. Nor would such an approach acknowledge how these two fields might, in turn, impact both real and perceived expectations, for example, on sample size requirements in studies on the development of genetic tests for customization of drug therapy. More in-depth and realistic projections of their codevelopment as a new hybrid and intellectually richer discipline necessitate self-reflection that extends beyond the classic disciplinary boundaries. Hence, although the fields of clinical pharmacogenomics and human genetics research are increasingly coalescing through technology and knowledge transfer, it is critical to discern the ways in which discipline-specific traditions, tacit knowledge, and expectations of practitioners may influence the course of scientific dialogue and collaboration at their disciplinary boundaries and interdisciplinary junctions.

As academic institutions move increasingly toward serving a dual role as engines for economic growth and a knowledge commons (research and teaching),[50–52] future public policy debates on pharmacogenomics, genetic testing, and personalized medicine will need to be reframed to incorporate these subtle but significant characteristics (see Table 1). Ultimately, the recognition that pharmacology is an experimental science should also elevate the ethical standards and accentuate the moral obligation to develop pharmacogenomic or other biomarkers prospectively before obtaining marketing approval. For drugs that have already been in clinical use, an equal effort should be made to facilitate

their targeted use for individuals and patient populations. Blockbuster drugs may increase the profits in selected cases, but they also unethically concentrate the risks of drug development in specific groups and communities.[53]

The expansion in scope of scientific research enabled by new genomic technologies may soon result in fragmented but more diversified and narrowly defined therapeutic fields or markets for drugs that will ultimately benefit patients while also shaping the varied expectations for long-term and sustainable growth in the pharmaceutical industry. This expansion also creates new control points and sociotechnical actors in academic research governance. By contextualizing genomic technologies as important technical and social sources of momentum that unites human geneticists and pharmacologists, one sees the future of personalized medicine or clinical pharmacogenomics contingent on often indeterminate or multifactorial events.[54,55] Yet while the future remains undecided and uncertain, there is arguably an actual ethical responsibility on the part of regulatory scientists, human genetics, molecular medicine, pharmacogenomics, and social science researchers to engage in a sustained interdisciplinary, open, accountable, and transparent dialogue aimed at the development of shared standards and science policies that demonstrate optimal methodologic rigor to favorably advance discoveries and serve the best interests of patients' and public health.

In increasingly overspecialized, hypercompetitive, and fragmented biomedical research with semantic and disciplinary discontinuities,[56,57] the only assurance for continuity and objectivity in interdisciplinary fields of inquiry (eg, pharmacogenomics) will thus depend on certain human qualities in scientific professional practice and, more broadly, in public health research. These qualities include an open recognition of our own discipline-specific biases and shortcomings, giving credence to (at least noticing) hitherto disenfranchised professional viewpoints and the boundaries surrounding each discipline or individual scientific methodologies.[58,59] Reductionist conceptual juxtapositions of one discipline next to another (ie, pharmacology and human disease genetics presented as pharmacogenomics) or borrowing technologies from one discipline and applying in another without adequate reflection, in the best of circumstances, may only lead to multidisciplinary summation of scientific inquiries. But this is not necessarily equivalent to interdisciplinary synthesis and reasoned reconciliation of norms at disciplinary intersections. It is only when we comfortably place ourselves in that interdisciplinary space and acknowledge the attendant semantic and methodologic uncertainties that we can begin to dispassionately learn from other disciplines while building a more certain and ethical future for pharmacogenomics, personalized medicine, and equitable public health policies.

Acknowledgments

We dedicate this article to our colleagues, Professors Werner Kalow and Laszlo Endrenyi (University of Toronto). Their interest in drivers of human cooperation at a population or group level and evolutionary biology helped shape our thinking on socially responsible corporate and academic research governance and their importance for equitable adoption of genomic medicine at the point of patient care.

All authors contributed to the development, interpretation, and synthesis of the ideas presented herein (from July 2004 to November 2006). The original idea for the asymmetry of inquiries between human genetics and pharmacology was conceived and contextualized by Ozdemir, Someya, Preskorn, and Friis at clinical pharmacology grand rounds at the Niigata University, Japan (April 2005), the National Institute of Mental Health–New Clinical Drug Evaluation Unit meeting (June 2005, FL), and the Summer Scholars Training Program at the VA Long Beach Healthcare System (August 2005). Ozdemir, Williams-Jones, Graham, Gripeos, Glatt, Reist, Szabo, and Lohr have discussed the need for targeted therapies, biomarker discovery, and validation before regulatory approval of pharmaceuticals, as well as the attendant importance of interdisciplinary dialogues for ensuring the application of targeted therapies that can actually serve the agenda of improving public health (in seminars at the University of California-San Diego Working Group on Personalized Medicine in Psychosis and, in part, at the Canadian Bioethics Society meeting in Halifax, October 2005). The ideas on framing pharmacology as an experimental science and how this may impact ethical, sociologic, and moral corollaries relating to the need for prospective clinical pharmacogenomic investigations were interpreted and synthesized to their final form by all authors.

Helpful discussions with the following colleagues are gratefully acknowledged: Lea Lowe, Mohammad Ali Farooq, Manabu Goseki, Carolina Rios-Mandel, Ralitza Abadjieva, Chris Gripeos, Ming T. Tsuang, and Kazutaka Shimoda.

References

1. Meyer UA. Pharmacogenetics—five decades of therapeutic lessons from genetic diversity. Nat Rev Genet 2004;5:669–76.

2. Kalow W. Pharmacogenetics and pharmacogenomics: origin, status, and the hope for personalized medicine. Pharmacogenomics J 2006;6:162–5.
3. Godard B, Marshall J, Laberge C, Knoppers BM. Strategies for consulting with the community: the cases of four large-scale genetic databases. Science and Engineering Ethics 2004;10:457–77.
4. Goldstein DB, Tate SK, Sisodiya SM. Pharmacogenetics goes genomic. Nat Rev Genet 2003;4:937–47.
5. Glatt SJ, Everall IP, Kremen WS, et al. Expression analysis of blood and brain provides concurrent validation of SELENBP1 up-regulation in schizophrenia. Proc Natl Acad Sci U S A 2005;102:15533–8.
6. Hedgecoe AM. Terminology and the construction of scientific disciplines: the case of pharmacogenomics. Sci Technol Human Values 2003;28:513–37.
7. Hedgecoe A, Martin P. The drugs don't work: expectations and the shaping of pharmacogenetics. Soc Stud Sci 2003;33: 327–64.
8. Ozdemir V, Lerer B. Pharmacogenomics and the promise of personalized medicine., In: Kalow W, Meyer UA, Tyndale RF, editors. Pharmacogenomics, 2nd expanded ed. New York: Marcel Dekker; 2005. p. 13–50.
9. Kalow W. Pharmacogenetics, pharmacogenomics, and pharmacobiology. Clin Pharmacol Ther 2001;70:1–4.
10. Szabo S, Glavin GB. Hans Selye and the concept of biologic stress. Ulcer pathogenesis as a historical paradigm. Ann N Y Acad Sci 1990;597:14–6.
11. Hopkins MM, Ibarreta D, Gaisser S, et al. Putting pharmacogenetics into practice. Nat Biotechnol 2006;24: 403–10.
12. Graham J. Diagnosing dementia: epidemiological and clinical data as cultural text., In: Leibing A, Cohen L, editors. Thinking about dementia. culture, loss and the anthropology of senility. Piscataway (NJ): Rutgers University Press; 2006.
13. Graham JE. Differentially diagnosing dementia: a triage of texts., In: Leibing A, Scheinkman L, editors. The diversity of Alzheimer's disease—different approaches and contexts. Rio de Janeiro: Edicoes IPUB/CUCA, Instituto de Psiquiatria; 2002.
14. MacKnight C, Graham JE, Rockwood K. Factors associated with inconsistent diagnosis of dementia between physicians and neuropsychologists. J Am Geriatr Soc 1999;47:1294–9.
15. Ozdemir V, Williams-Jones B, Glatt SJ, et al. Shifting emphasis from pharmacogenomics to theragnostics: what will be the role of theragnostic patents in upstream and downstream biomarker research? Nat Biotechnol 2006;28: 942–6.
16. Need AC, Motulsky AG, Goldstein DB. Priorities and standards in pharmacogenetic research. Nat Genet 2005;37: 671–81.
17. de Leon J. AmpliChip CYP450 test: personalized medicine has arrived in psychiatry. Expert Rev Mol Diagn 2006;6: 277–86.
18. Godard B, Schmidtke J, Cassiman JJ, Ayme S. Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective. Eur J Hum Genet 2003;11 Suppl 2:S88–122.
19. Corrigan OP, Williams-Jones B. Pharmacogenetics: the bioethical problem of DNA investment banking. Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences 2006;37:549–64.
20. Preskorn SH. Multiple medication use in patients seen in the Veterans Affairs healthcare system: so what? J Psychiatr Pract 2005;11:46–50.
21. Drews J. Drug discovery: a historical perspective. Science. 2000;287:1960–4.
22. Ozdemir V, Kalow W, Tothfalusi L, et al. Multigenic control of drug response and regulatory decision-making in pharmacogenomics: the need for an upper-bound estimate of genetic contributions. Curr Pharmacogenomics 2005;3: 53–71.
23. Friis RH, Seller TA. Epidemiology for public health practice. Boston: Jones & Bartlett Publishers; 2003.
24. Kalow W, Tang BK, Endrenyi L. Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. Pharmacogenetics 1998;8: 283–9.
25. Kalow W, Ozdemir V, Tang BK, et al. The science of pharmacological variability: an essay. Clin Pharmacol Ther 1999;66:445–7.
26. Leabman MK, Giacomini KM. Estimating the contribution of genes and environment to variation in renal drug clearance. Pharmacogenetics 2003;13:581–4.
27. Velasque LS, Estrela Rde C, Suarez-Kurtz G, Struchiner CJ. Estimating the genetic component (RGC) in pharmacokinetic variability of the antiretroviral didanosine among healthy Brazilians. AIDS 2005;19 Suppl 4:S76–80.
28. Corrigan OP. A risky business: the detection of adverse drug reactions in clinical trials and post-marketing exercises. Soc Sci Med 2002;55:497–507.
29. Williams-Jones B, Ozdemir V. Enclosing the 'knowledge commons': patenting genes for disease risk and drug response at the university-industry interface. In: Lenk C, Hoppe N, Andorno R, editors. Ethics and law of intellectual property. Current problems in politics, science and technology. London: Ashgate Publishing; 2006. p. 177–209.
30. Ozdemir V, Williams-Jones B, Cooper DM, et al. Mapping translational research in the age of theragnostics: from molecular markers to personalized drug therapy. Pharmacogenomics 2006. [In press].
31. Williams-Jones B, Corrigan OP. Rhetoric and hype: where's the 'ethics' in pharmacogenomics? Am J Pharmacogenomics 2003;3:375–83.
32. Eisenberg RS. Will pharmacogenomics alter the role of patents in drug development? Pharmacogenomics 2002;3: 571–4.
33. Hedgecoe A. The politics of personalised medicine-pharmacogenetics in the clinic. Cambridge studies in society and the life sciences. Cambridge (UK): Cambridge University Press; 2004.

34. Sherrid P. Designer drugs. What's best for patients isn't always what's best for profits. US News & World Report 2001;131:30–2.
35. Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services. Available at: http://www.fda.gov/cder/rdmt/pstable.htm (accessed November 20, 2006).
36. Angell M. Excess in the pharmaceutical industry. CMAJ 2004;171:1451–3.
37. Service RF. Surviving the blockbuster syndrome. Science 2004;303:1796–9.
38. Lucier C, Schuyt R, Tse E. CEO succession 2004. The world's most prominent temp workers. Strategy+Business 2005. Available at: http://www.strategy-business.com/media/file/sb39_05204.pdf) (accessed November 20, 2006).
39. Kelly M. The incredibly unproductive shareholder. Harv Bus Rev 2002;80:18–9.
40. Charan R. Ending the CEO succession crisis. Harv Bus Rev 2005;83:72–81.
41. Brown N. Hope against hype—accountability in biopasts, presents and futures. Sci Stud 2003;16:3–21.
42. Williams-Jones B, Ozdemir V. Challenges for corporate ethics in marketing genetic tests. J Business Ethics 2007. [In press].
43. Graham J. Smart regulation: will the government's strategy work? CMAJ 2005;173:1469–70.
44. Wood AJ. The safety of new medicines: the importance of asking the right questions. JAMA 1999;281:1753–4.
45. Dwyer J. Global health and justice. Bioethics 2005;19:460–75.
46. MacDonald C. Business ethics 101 for the biotech industry. BioDrugs 2004;18:71–7.
47. Dhanda RK. Guiding Icarus: merging bioethics with corporate interests.. New York: Wiley-Liss; 2002.
48. Dhanda RK. Bioethics in biotechnology: from pain to gain. Drug Dev Res 2004;63:93–102.
49. David PA, Foray D. An introduction to the economy of the knowledge society. Int Soc Sci J 2002;54:9–23.
50. Etzkowitz H, Webster A, Gebhardt C, Cantisano-Terra BR. The future of the university and the university of the future: evolution of ivory tower to entrepreneurial paradigm. Res Policy 2000;29:313–30.
51. Williams-Jones B. Knowledge commons or economic engine—what's a university for? J Med Ethics 2005;31:249–50.
52. Atkinson-Grosjean J. Public science, private interests: culture and commerce in Canada's networks of centres of excellence. Toronto: University of Toronto Press; 2006.
53. Corrigan OP. 'First in man': the politics and ethics of women in clinical drug trials. Feminist Review 2002;72:40–52.
54. Casti JL. Searching for certainty: what scientists can know about the future. New York: William Morrow and Co.; 1990.
55. Prigione I, Isabelle S. Order out of chaos. London: Harper Collins; 1985.
56. Dubochet J. Making science in a fractal landscape. Micron 2001;32:7–9.
57. Kalow W. The Pennsylvania State University College of Medicine 1990 Bernard B. Brodie Lecture. Pharmacogenetics: past and future. Life Sci 1990;47:1385–97.
58. Ozdemir V, Williams-Jones B. Democracy unleashed: unpacking the tooth fairy in drug industry R&D. Nat Biotechnol 2006;24:1324–6.
59. Foucault M. Subjectivity and truth. In: Rabinow P, editor. Michel Foucault ethics: subjectivity and truth. Essential works of Foucault, 1954–1984. New York: The New Press; 1997. p. 87–92.

8

Dose-Dependent Effects of the 3435 C>T Genotype of *ABCB1* Gene on the Steady-State Plasma Concentration of Fluvoxamine in Psychiatric Patients

Naoki Fukui, MD, Yutaro Suzuki, MD, PhD,* Kazushi Sawamura, MD, PhD,* Takuro Sugai, MD,* Junzo Watanabe, MD,* Yoshimasa Inoue,† and Toshiyuki Someya, MD, PhD**

Abstract: This study investigated effects of the 3435 C>T genotype of the adenosine triphosphate–binding cassette subfamily B member 1 (ABCB1, MDR1) gene on the steady-state plasma concentration of fluvoxamine (FLV).

Methods: Sixty-two psychiatric patients were treated with different doses (50, 100, 150, and 200 mg/d) of FLV. Blood samples were collected after at least 2 weeks of treatment with the same daily dose to obtain steady-state concentrations of FLV, and 3435 C>T genotype was determined by polymerase chain reaction.

Results: FLV concentration-to-dose ratio was significantly different among 3435 C>T genotype groups at the 200 mg/d dose ($P = 0.019$). A post-hoc analysis revealed that FLV concentration-to-dose ratio was significantly higher in the TT genotype group as compared with the CC genotype group at the 200 mg/d dose (median value of concentration-to-dose ratio (ng/mL)/(mg/d), 0.861 vs 0.434, $P = 0.026$). FLV concentration-to-dose ratio was significantly higher in the CT + TT genotype group than the CC genotype group at the 200 mg/d dose (median value of concentration-to-dose ratio (ng/mL)/(mg/d), 0.618 vs 0.434, $P = 0.031$). At 50, 100, and 150 mg/d dose, FLV concentration-to-dose ratios were not significantly different among 3435 C>T genotype groups. At 50, 100, and 150 mg/d dose, no significant differences were found in FLV concentration-to-dose ratios between the CT + TT genotype group and CC genotype group.

Conclusions: This study suggests that pharmacokinetics of FLV depend on *ABCB1* gene polymorphism only at the 200 mg/d dose.

Key Words: ABCB1 (MDR1/P-glycoprotein), gene polymorphism, antidepressants, SSRIs, plasma fluvoxamine concentration

(*Ther Drug Monit* 2007;0:000–000)

INTRODUCTION

Fluvoxamine (FLV) is a selective serotonin reuptake inhibitor (SSRI), which is used not only for the treatment of depression but also for the treatment of a variety of other psychiatric disorders, such as panic disorder, social anxiety disorder, and obsessive-compulsive disorder. Several studies have shown cytochrome-P450 (CYP) 1A2[1,2] and CYP2D6[2,3] to have a significant impact on FLV pharmacokinetics. However, other studies reported that CYP1A2[4] and CYP2D6[4,5] had no major effects on plasma FLV concentrations. The specific factors involved in the pharmacokinetics of FLV have not been clearly identified.

The adenosine triphosphate (ATP)-binding cassette subfamily B member 1 (ABCB1), which is also known as MDR1 or P-glycoprotein, is an integral membrane protein of 170 Kd and belongs to the ATP-binding cassette superfamily of membrane transporters. It serves as a potent ATP-dependent efflux pump for a wide variety of lipophilic compounds. Overexpression of ABCB1 in tumor cells confers the commonly known phenomenon of multidrug resistance against antineoplastic agents.[6,7] ABCB1 is also expressed in normal tissues such as liver, kidney, and intestine where it contributes to the elimination of xenobiotics and drugs into bile and urine or limits drug absorption from the gastrointestinal tract.[8,9]

Hoffmeyer et al[10] reported that a single nucleotide polymorphism (3435 C>T) in exon 26 of *ABCB1* gene was associated with duodenal expression of ABCB1 and associated function in humans. Carriers homozygous for this polymorphism (TT) showed more than a 2-fold lower ABCB1 expression and higher digoxin plasma concentration than the CC group. Several studies also have reported that the T allele of 3435 C>T relates to higher concentrations of drugs such as digoxin,[10,11] cyclosporine A,[12,13] and tacrolimus.[14]

Penetration of amitriptyline into the brain was enhanced in mice lacking P-glycoprotein.[16] The 3435 C>T genotype was also associated with the occurrence of nortriptyline-induced postural hypotension.[17] These studies suggested that ABCB1 might affect the pharmacokinetics of antidepressants. However, there have been few clinical studies investigating effects of the functional status of ABCB1 on pharmacokinetics of antidepressants. In this study, we investigated effects of the *ABCB1* gene polymorphism on steady-state plasma concentration of FLV in patients treated with different doses of FLV.

MATERIALS AND METHODS

Subjects

This study was approved by the Ethics Committee on Genetics of Niigata University School of Medicine.

Received for publication September 20, 2006; accepted December 15, 2006.
From the *Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; and †MP-Technopharma Corporation Technology Department, Fukuoka, Japan.
Reprints: Toshiyuki Someya, MD, PhD, Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, 757 Asahimachidori-ichibancho, Niigata 951-8510, Japan (e-mail: someya@med.niigata-u.ac.jp).

All patients received an explanation of the objectives of the study, and only those who gave written consent to participate in this study were enrolled. Demographic data; medical history; and laboratory data including hematology, serology, electrolytes, and urine analysis were collected for each patient. Patients with obvious physical illness were excluded. Patients older than 65 years of age and those younger than 20 years of age were excluded. Smokers (≥20 cigarettes/day) were also excluded because smoking is known to induce the CYP1A2 enzyme and increases the metabolisms of drugs eliminated by this enzyme. Patients concomitantly treated with other drugs, except some benzodiazepines, were excluded. The subjects included 62 Japanese outpatients (25 females and 37 males). The mean age ± standard deviation (SD) was 36.2 ± 11.9 years. Their diagnoses were major depressive disorder (n = 55), dysthymic disorder (n = 1), depressive disorder not otherwise specified (n = 1), bipolar disorder (n = 1), anxiety disorder (n = 1), bulimia nervosa (n = 1), and adjustment disorder (n = 2), according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision.[18] The subjects received FLV in 2 equally divided doses at 9:00 and 21:00.

Blood Sampling

Patients were maintained on the same daily doses of FLV for at least 2 weeks to obtain steady-state concentrations of FLV. Blood sampling was done using a Venoject tube with ethylene tetraacetic acid (EDTA)-Na (Terumo Japan, Tokyo, Japan) 12 hours after the last dosage. Within 2 hours of collection, samples were centrifuged at 3,000 g and aliquots of plasma were drawn out in pipettes for determining plasma levels of fluvoxamine with samples stored at –80°C until assayed.

Determination of Drug Plasma Concentration

Plasma FLV concentration was measured using column-switching high-performance liquid chromatography with ultraviolet detection. Drugs in plasma to which cisapride had been added as an internal standard were extracted with hexane-chloroform. The extract was subjected to an automated column-switching high-performance liquid chromatography using a TSK BSA-C8 precolumn (Tosoh, Tokyo, Japan) for sample cleanup and a TSK gel ODS-80TS column (Tosoh) for separation.

Calibration curves (n = 6) were linear over the concentration ranging from 1.2 to 150 ng/mL ($r > 0.999$) for FLV. Intraday (n = 6) and between-days (n = 6) coefficients variations determined at 3 different concentrations (2.5, 38, and 150 ng/mL) were less than 4.7% and 3.9%, respectively. Recoveries and their coefficients variations (n = 6) determined at 3 different concentrations (1.25, 25, and 100 ng/mL) were 94.9–97.3%, and less than 1%, respectively. The limit of quantification (signal/noise ratio = 5) was 1.0 ng/mL.

Genotyping

Genomic DNA was extracted from peripheral blood using a QIA-amp Blood Kit (Qiagen, California). 3435 C>T of *ABCB1* were genotyped using the TaqMan 5'-exonuclease assay. Primer and probe sets were designed and synthesized by Applied Biosystems (Foster City, California). Polymerase chain reaction amplification was preformed using TaqMan 2x Universal Master Mix, No AmpErase UNG (Applied Biosystems), 5 ng of DNA, 0.9 μmol/L of each primer, and 200 nmol/L of each probe in total volume of 5 μL. Thermal cycler conditions were 95°C for 10 minutes, 40 cycles of 92°C for 15 seconds, and 60°C for 1 minute. Fluorescence and allelic discrimination were measured with a ABI PRISM 7900HT Sequence Detection System using SDS 2.0 software (Applied Biosystems).

Statistical Analysis

Statistical analysis was conducted with the SPSS II software for Windows (SPSS Japan Inc, Tokyo, Japan). A Mann-Whitney test was used to detect differences in FLV concentration-to-dose ratio between 50 mg/d and 200 mg/d dose treatment groups. Comparison of mean age among 3435 C>T genotypes was performed by analysis of variance (ANOVA) with the Bonferroni's test used as a post-hoc test. Differences in gender distribution among 3435 C>T genotypes were compared with the χ^2-test. Differences in FLV concentration-to-dose ratio among 3435 C>T genotypes were compared using the Kruskal-Wallis analysis with the Scheffe's test used as post-hoc test. Differences in FLV concentration-to-dose ratio between 2 genotype groups were compared by a Mann-Whitney test. A nonparametric ranking sum test (Friedman test) was used to detect differences in FLV concentration-to-dose ratio among 4 doses of FLV. Level of statistical significance was set at $P < 0.05$.

RESULTS

Of the 62 patients, 15 patients had data of FLV concentration at 1 dose, 15 patients had it at 2 different doses, 12 patients had it at 3 different doses, and 20 patients had at it 4 different doses of FLV. Median value of FLV concentration-to-dose ratio was 0.282 (50 mg/d, n = 49), 0.381 (100 mg/d, n = 42), 0.477 (150 mg/d, n = 40), and 0.554 (ng/mL)/(mg/d) (200 mg/d, n = 30); it significantly increased with increasing daily dose (50 gm/d vs 200 mg/d, $P < 0.001$).

3435 C>T genotype frequency was 0.31 (n = 19) for CC, 0.55 (n = 34) for CT, and 0.15 (n = 9) for TT. Genotype frequency was not significantly different from the values expected from the Hardy-Weinberg equilibrium ($\chi^2 = 0.99$, $P = 0.32$, df = 2).

In the 50, 100, 150, and 200 mg/d dose treatment groups, there were no significant differences among 3435 C>T genotype groups regarding mean age (P = 0.23, 0.35, 0.27, and 0.09, respectively; Table 1) or gender distribution (P = 0.08, 0.18, 0.29, and 0.08, respectively; Table 1). Furthermore, there were no significant sex-related differences in plasma FLV concentration at any doses (data not shown). T1

FLV concentration-to-dose ratio was significantly different among 3435 C>T genotype groups at the 200 mg/d dose ($P = 0.019$; Table 1). A post-hoc analysis revealed that FLV concentration-to-dose ratio was significantly higher in the TT genotype group than that in the CC genotype group at 200 mg/d dose ($P = 0.026$; Table 1). FLV concentration-to-dose

TABLE 1. Demographics and FLV Concentration-to-Dose Ratio (ng/mL)/(mg/d) of Subjects Classified by *ABCB1* Genotypes

	50 mg/d			100 mg/d		
	CC	CT	TT	CC	CT	TT
Number of subjects	13	29	7	12	25	5
Female/male	6/7	8/21	5/2	6/6	9/16	4/1
Age (year ± SD)	38.3 ± 12.7	37.7 ± 12.1	36.6 ± 12.0	37.8 ± 10.7	35.7 ± 11.5	28.6 ± 5.0
FLV concentration*						
Median	0.268	0.250	0.350	0.391	0.337	0.556
Range	0.088–0.762	0.032–0.776	0.210–0.832	0.105–0.825	0.058–1.888	0.277–2.172
Kruskal-Wallis test		$P = 0.15$			$P = 0.24$	
	150 mg/d			200 mg/d		
	CC	CT	TT	CC	CT	TT
Number of subjects	11	23	6	10	16	4
Female/male	6/5	8/15	4/2	5/5	6/10	4/0
Age (year ± SD)	35.4 ± 8.4	36.9 ± 12.3	28.3 ± 4.5	36.5 ± 6.2	35.2 ± 13.2	27.3 ± 4.6
FLV concentration*						
Median	0.411	0.433	0.548	0.434	0.603	0.861†
Range	0.196–1.009	0.104–2.241	0.255–2.858	0.188–0.667	0.088–2.042	0.588–3.395
Kruskal-Wallis test		$P = 0.55$			$P = 0.019$	

FLV, fluvoxamine; *ABCB1*, ATP-binding cassette subfamily B member 1 gene; SD, standard deviation.
*Concentration-to-dose ratio (ng/mL)/(mg/d).
†Post-hoc analysis revealed that plasma FLV concentration was significantly higher in the TT group than that in the CC group ($P = 0.026$).

ratio was significantly higher in the CT + TT genotype group than in the CC genotype group at the 200 mg/d dose (median value of concentration-to-dose ratio (ng/mL)/(mg/d), 0.618 vs 0.434, $P = 0.031$).

At 50, 100, and 150 mg/d dose, FLV concentration-to-dose ratios were not significantly different among C3435T genotype groups (Table 1). At 50, 100, and 150 mg/d dose, there was no significant difference in FLV concentration-to-dose ratio between the CT + TT genotype and CC genotype groups ($P = 0.96$, 0.91, and 0.55, respectively).

T2 Table 2 shows FLV concentration-to-dose ratios of 20 patients tested at all 4 doses. In these 20 patients, FLV concentration-to-dose ratios significantly increased with increasing daily dose (Table 2). At 50, 100, 150, and 200 mg/d dose, FLV concentration-to-dose ratios were not significantly different among 3435 C>T genotype groups (Table 2). At 50, 100, 150, and 200 mg/d dose, subjects with the TT genotype of 3435 C>T had higher FLV concentration-to-dose ratios than those from the CC + CT genotype group ($P = 0.038$, 0.12, 0.13, and 0.038, respectively).

DISCUSSION

This study suggested that the 3435 C>T genotype in *ABCB1* had a significant effect on steady-state plasma concentration of FLV only at a treatment dose of 200 mg/d. Subjects with the TT genotype of 3435 C>T showed a significantly higher FLV concentration-to-dose ratio than that of subjects with the CC genotype at the 200 mg/d. Although not statistically significant, heterozygous (CT) subjects tended to have higher FLV concentration-to-dose ratios than that of CC subjects at the 200 mg/d dose. This result was consistent with those of Hoffmeyer et al's findings that showed subjects with the CC genotype of 3435 C>T had high intestinal ABCB1 expression and low digoxin concentration in contrast to TT subjects with low intestinal ABCB1 expression and high

TABLE 2. FLV Concentration-to-Dose Ratio (ng/mL)/(mg/d) of 20 Patients Tested at All 4 Doses

ABCB1 Genotype	50 mg/d		100 mg/d		150 mg/d		200 mg/d	
	Median	[Range]	Median	[Range]	Median	[Range]	Median	[Range]
All (n = 20)	0.284*	[0.048–0.832]	0.474*	[0.085–2.172]	0.526*	[0.104–2.858]	0.580*	[0.088–3.395]
CC (n = 5)	0.252	[0.164–0.338]	0.359	[0.132–0.528]	0.411	[0.196–0.751]	0.501	[0.187–0.667]
CT (n = 11)	0.250	[0.048–0.550]	0.458	[0.085–0.899]	0.464	[0.104–0.986]	0.572	[0.088–1.091]
TT (n = 4)	0.476	[0.310–0.832]	0.626	[0.467–2.172]	0.731	[0.490–2.858]	0.861	[0.588–3.395]
Kruskal-Wallis test	$P = 0.091$		$P = 0.18$		$P = 0.25$		$P = 0.072$	

FLV, fluvoxamine; *ABCB1*, ATP-binding cassette subfamily B member 1 gene.
*FLV concentration-to-dose ratio significantly increased with increasing daily dose ($P < 0.001$, Friedman test).

AU1 digoxin concentration, whereas heterozygous (CT) subjects presented with intermediate levels.[10] Our additional analysis of 20 patients tested at all 4 doses also suggested that TT subjects have higher FLV concentration-to-dose ratio compared with CC or CT subjects, although the number of subjects was small and dose-dependent effects of the 3435 C>T genotype could not be detected clearly.

Two studies[2,3] using a single oral dose of 50 mg FLV reported that the area under the plasma or serum concentration-time curve (area under the curve, or AUC) of FLV was significantly associated with CYP2D6 activity. A significant correlation between AUC of FLV and CYP1A2 activity was found in 1 study using a single oral dose of 50 mg FLV.[1] These studies suggested that pharmacokinetics of FLV depended on CYP2D6 and CYP1A2 activity at lower doses such as 50 mg FLV. However, a 2003 study[4] using 200 mg/d FLV did not find effects of CYP1A2 and CYP2D6 on the pharmacokinetics of FLV, and the possible explanation for this result was thought to be saturation of CYP1A2 and CYP2D6 at high doses of FLV. Saturation kinetics of CYP2D6 have been demonstrated for other drugs such as paroxetine.[19] CYP1A2 has also been characterized by saturation kinetics for other drugs such as theophylline[20] and caffeine.[21] Several other studies[22–24] have shown nonlinear kinetics for FLV, which is considered to be caused by the saturation of CYP1A2 and CYP2D6. In our study, FLV concentration-to-dose ratio also increased with increasing treatment dose. The 3435 C>T genotype had a significant effect on plasma FLV concentration only at the highest dose of FLV, 200 mg/day, likely because of an increasing number of subjects with saturated CYP1A2 and CYP2D6 at this higher dose.

An in vitro study[25] suggested that FLV had an ABCB1 inhibitory effect. Therefore, ABCB1 may be partly involved in nonlinear kinetics of FLV, and ABCB1 inhibitory effect of FLV may be different among *ABCB1* genotype groups. However, our study did not investigate these points.

As mentioned earlier, several reports have suggested that CYP2D6 is involved in the metabolism of FLV. Several mutated alleles of the *CYP2D6* gene causing absent activity such as *3, *4, and *5, and decreased activity such as *10, have been reported. Accordingly, in subjects having mutated alleles of CYP2D6, the CYP2D6 pathway may be easily saturated at relatively lower doses, and ABCB1 has a greater impact on FLV metabolism. Further studies analyzing genotype of *ABCB1* with that of *CYP2D6* are needed to investigate FLV pharmacokinetics in details.

The 3435 C>T polymorphism genotyped in our study causes no amino acid change. There may be other functional polymorphisms in significant linkage disequilibrium with 3435 C>T polymorphism that affect the pharmacokinetics of FLV. For instance, the G2677A/T polymorphism in exon 21 causes an amino acid change and is associated with expression of P-glycoprotein.[26,27] This polymorphism is found to be in significant linkage disequilibrium with 3435 C>T polymorphism.[26] Further studies investigating other polymorphisms including G2677A/T are needed.

In addition, it would be interesting to investigate effects of *ABCB1* gene polymorphisms on FLV pharmacokinetics at doses higher than 200 mg/d because high doses of SSRIs are occasionally needed to obtain a therapeutic effect in the treatment of psychiatric disorders such as obsessive-compulsive disorder.

CONCLUSION

This study suggests that pharmacokinetics of FLV depend on 3435 C>T genotype of *ABCB1* at high doses such as 200 mg/d. However, sample size of the present was quite small, and only 4 subjects carried the TT genotype of 3435 C>T in the 200 mg/d treatment group. Further studies with a larger sample size are needed to clarify the extent of involvement of *ABCB1* gene polymorphism on FLV pharmacokinetics.

ACKNOWLEDGMENTS

This research was supported by Health and Labour Sciences Research Grants (Research on Psychiatric and Neurological Disease and Mental Health) (H17-kokoro-002), and by Grant-in-Aid for Young Scientists (B). We would like to express our deep gratitude to all of the patients. We also thank Hiroshi Kusano and Tomoko Yamada for their excellent technical assistance.

REFERENCES

1. Spigset O, Carleborg L, Hedenmalm K, et al. Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. *Clin Pharmacol Ther.* 1995;58:399–403.
2. Carrillo JA, Dahl ML, Svensson JO, et al. Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. *Clin Pharmacol Ther.* 1996;60:183–190.
3. Spigset O, Granberg K, Hägg S, et al. Relationship between fluvoxamine pharmacokinetics and CYP2D6/CYP2C19 phenotype polymorphisms. *Eur J Clin Pharmacol.* 1997;52:129–133.
4. Gerstenberg G, Aoshima T, Fukasawa T, et al. Effects of the CYP2D6 genotype and cigarette smoking on the steady-state plasma concentration of fluvoxamine and its major metabolite fluvoxamino acid in Japanese depressed patients. *Ther Drug Monit.* 2003;25:463–468.
5. Ohara K, Tanabe S, Ishibashi K, et al. CYP2D6*10 alleles do not determine plasma fluvoxamine concentration/dose ratio in Japanese subjects. *Eur J Clin Pharmacol.* 2003;58:659–661.
6. Gottesman MM, Pastan I, Ambudkar SV. P-glycoprotein and multidrug resistance. *Curr Opin Genet Dev.* 1996;6:610–617.
7. Ambudkar SV, Dey S, Hrycyna CA, et al. Biochemical, cellular, and pharmacological aspects of the multidrug transporter. *Annu Rev Pharmacol Toxicol.* 1999;39:361–398.
8. Tanigawara Y. Role of P-glycoprotein in drug disposition. *Ther Drug Monit.* 2000;22:137–140.
9. Terao T, Hisanaga E, Sai Y, et al. Active secretion of drugs from the small intestinal epithelium in rats by P-glycoprotein functioning as an absorption barrier. *J Pharm Pharmacol.* 1996;48:1083–1089.
10. Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: Multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. *Proc Natl Acad Sci USA.* 2000;97:3473–3478.
11. Kurata Y, Ieiri I, Kimura M, et al. Role of human MDR1 gene polymorphism in bioavailability and interaction of digoxin, a substrate of P-glycoprotein. *Clin Pharmacol Ther.* 2002;72:209–219.
12. Verstuyft C, Schwab M, Schaeffeler E, et al. Digoxin pharmacokinetics and MDR1 genetic polymorphisms. *Eur J Clin Pharmacol.* 2003;58:809–812.
13. Chowbay B, Cumaraswamy S, Cheung YB, et al. Genetic polymorphisms in MDR1 and CYP3A4 genes in Asians and the influence of MDR1 haplotypes on cyclosporin disposition in heart transplant recipients. *Pharmacogenetics.* 2003;13:89–95.

14. Bonhomme-Faivre L, Devocelle A, Saliba F, et al. MDR1 C3435T polymorphism influences cyclosporine A dose requirement in liver-transplant recipients. *Transplantation.* 2004;78:21–25.
15. Zheng H, Webber S, Zeevi A, et al. Tacrolimus dosing in pediatric heart AU2 transplant patients is related to CYP3A5 and NDR1 gene polymorphisms. *Am J Transplant.* 2003;3:477–483.
16. Uhr M, Steckler T, Yassouridis A, et al. Penetration of amitriptyline, but not of fluoxetine, into brain is enhanced in mice with blood-brain barrier deficiency due to mdr1a P-glycoprotein gene disruption. *Neuropsychopharmacology.* 2000;22:380–387.
17. Roberts RL, Joyce PR, Mulder RT, et al. A common P-glycoprotein polymorphism is associated with nortriptyline-induced postural hypotension in patients treated for major depression. *Pharmacogenomics J.* 2002; 2:191–196.
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Text Revision. APA: Washington, DC; 2000.
19. Sawamura K, Suzuki Y, Someya T. Effects of dosage and CYP2D6-mutated allele on plasma concentration of paroxetine. *Eur J Clin Pharmacol.* 2004;60:553–557.
20. Dahlqvist R, Billing B, Miners JO, et al. Nonlinear metabolic disposition of theophylline. *Drug Monit.* 1984;6:290–297.
21. Kamimori GH, Lugo SI, Penetar DM, et al. Dose-dependent caffeine pharmacokinetics during severe sleep deprivation in humans. *Int J Clin Pharmacol Ther.* 1995;32:182–186.
22. Härtter S, Wetzel H, Hiemke C. Automated determination of fluvoxamine in plasma by column-switching high-performance liquid chromatography. *Clin Chem.* 1992;38:2082–2086.
23. Spigset O, Öhman R. A case of fluvoxamine intoxication demonstrating nonlinear elimination pharmacokinetics. *J Clin Psychopharmacol.* 1996; 16:254–255.
24. Spigset O, Granberg K, Hägg S, et al. Non-linear fluvoxamine disposition. *Br J Clin Pharmacol.* 1998;45:257–263.
25. Weiss J, Dormann SK, Martin-Facklam M, et al. Inhibition of P-glycoprotein by newer antidepressants. *J Pharmacol Exp Ther.* 2003; 305:197–204.
26. Tanabe M, Ieiri I, Nagata N, et al. Expression of P-glycoprotein in human placenta: Relation to genetic polymorphism of the multidrug resistance (MDR)-1 gene. *J Pharmacol Exp Ther.* 2001;297:1137–1143.
27. Siegmund W, Ludwig K, Giessmann T, et al. The effects of the human MDR1 genotype on the expression of duodenal P-glycoprotein and disposition of the probe drug talinolol. *Clin Pharmacol Ther.* 2002;72: 572–583.

そこが知りたい

薬物療法 Q&A

横山 裕一　渡部雄一郎　染矢 俊幸
新潟大学大学院医歯学総合研究科
精神医学分野

Q 非定型抗精神病薬は強迫症状を惹起するか？

A これまでいくつかの研究により強迫性障害（obsessive-compulsive disorder, OCD）に対してセロトニン再取り込み阻害薬（serotonin reuptake inhibiter, SRI）と非定型抗精神病薬（非定型薬）との併用が有効であることが確認されている[18]。しかし，その一方でclozapine（CLZ）[1,3-7,14-16]，olanzapine（OLZ）[12,13]，risperidone（RIS）[10,17]，quetiapine（QTP）[9]などの非定型薬が強迫症状を惹起あるいは悪化させることが報告されている。

CLZに関して，de Haanらは最近発症した若い統合失調症および他の精神病性障害の入院患者を対象とした後方視的な調査を行い，強迫症状の出現や悪化は，CLZ群（34人）が20.0%，他の抗精神病薬群（77人）が1.3%とCLZ群で有意に多く，強迫症状に対してはCLZの減量あるいはparoxetineやfluoxetine（FLX）など選択的セロトニン再取り込み阻害薬（selective SRI, SSRI）との併用が有効であったとしている[6]。CLZの症例報告は他の非定型薬に比べて最も多くみられ，診断は全例が統合失調症であり，CLZ投与により陽性症状や陰性症状が改善した後に，洗浄や確認など様々な強迫症状が出現あるいは悪化したとされている。CLZの使用量は150～900mg/日[3,16]と報告によって様々であり，強迫症状出現までの期間は1～6ヵ月程度の報告が多くみられたが，CLZ開始2年後に初めて強迫症状が確認されたとする例もある[16]。治療としてはCLZの減量のみで強迫症状が軽快したとするもの[5]や，FLX[4,14]，sertraline[1,16]，clomipramine（CMI）[3,5]などの(S)SRIを併用することにより改善したとする例が多くみられる。反対にCLZと強迫症状との関連を否定する報告もあり，Ghaemiらは入院後にCLZの投与を開始された142人の患者（統合失調症41人，失調感情障害52人，双極性障害20人，大うつ病性障害11人，その他18人）を対象として後方視的な調査を行った結果，CLZと強迫症状との関連は認めなかったとしている[8]。しかしこの研究では対象における統合失調症の割合が少なく，これまでの症例報告がほとんど統合失調症であることと一致していないという反論もなされている[6]。

OLZに関してもCLZと同様に，OLZ 10mg，15mg，25mg/日の投与開始後それぞれ4週，14日，3ヵ月で強迫症状が確認され，fluvoxamine（FLV），CMI，FLXの併用で改善した統合失調症の症例などの報告がなされている[12,13]。一方，Bakerらは慢性期統合失調症の入院患者25人を，placebo群（7人），OLZ 1 mg/日投与群（11人），OLZ 10mg/日投与群（7人）に無作為に割付け，6週間の二重盲検比較試験を行った。OLZの投与期間が十分ではなかった可能性はあるものの，OLZと強迫症状の出現や悪化には関連はなかったとしている[2]。これに対してOLZの用量も不十分なのではないかという意見[6]もあり，今後の大規模な研究が必要と考えられる。

RISにおいては，4 mg/日を開始し3週後に強迫症状が出現した1例[17]や，6 mg/日開始後3週で強迫症状が出現しFLV100mg/日の併用で改善した統合失調症[10]が報告されている。

QTPに関して，Khullarらは OCD，抜毛癖，双極Ⅱ型障害，妄想性障害と診断されていた43歳男性の妄想に対して，QTP 50mg/日を開始したところ3週間後から強迫症状が悪化し，QTPの中止により2週間後には元のレベルまで改善したと報告している[9]。

以上，大多数の症例報告では統合失調症や類縁の精神病性障害の患者で，非定型薬使用後に陽性症状や陰性症状は軽減するものの，強迫症状が出現あるいは悪化したとしており，治療としては非定型薬の減量あるいは(S)SRIの併用が選択され効果が得られている。非定型薬ではドパミンD_2受容体遮断作用よりもセロトニン5-HT_{2A}受容体阻害作用が強く，これにより強迫症状が惹起あ

るいは悪化すると推察されている[3,11,14,15]。

結　論

OCDにおける強迫症状に対してはSSRI単剤での治療効果が十分ではない場合に，非定型薬を併用することによって有効な治療効果が得られる一方，統合失調症をはじめとする精神病性障害の患者では非定型薬が強迫症状を惹起あるいは悪化させる可能性が示唆されており，その機序として5-HT_{2A}受容体拮抗作用が考えられている。しかし現時点では未だエビデンスのレベルが低く，今後さらなる研究の蓄積が期待される。

文　献

1) Allen, L., Tejera, C.: Treatment of clozapine-induced obsessive-compulsive symptoms with sertraline [letter]. Am. J. Psychiatry, 151: 1096–1097, 1994.
2) Baker, R. W., Ames, D., Umbricht, D. S. G. et al.: Obsessive-compulsive symptoms in schizophrenia: a comparison of olanzapine and placebo. Psychopharmacol. Bull., 32: 89–93, 1996.
3) Biondi, M., Fedele, L., Arcangeli, T. et al.: Development of obsessive-compulsive symptoms during clozapine treatment in schizophrenia and its positive response to clomipramine [letter]. Psychother. Psychosom., 68: 111–112, 1999.
4) Cassady, S. L., Thaker G. K.: Addition of fluoxetine to clozapine [letter]. Am. J. Psychiatry, 149: 1274, 1992.
5) Cheung, E. F. C.: Obsessive-compulsive symptoms during treatment with clozapine in a patient with schizophrenia. Aust. N. Z. J. Psychiatry, 35: 695–696, 2001.
6) de Haan, L., Linszen, D. H., Gorsira, R.: Clozapine and obsessions in patients with recent-onset schizophrenia and other psychotic disorders. J. Clin. Psychiatry, 60: 364–365, 1999.
7) Eales, M. J., Layeni, A. O.: Exacerbation of obsessive-compulsive symptoms associated with clozapine. Br. J. Psyciatry, 164: 687–688, 1994.
8) Ghaemi, S. N., Zarate, C. A., Popli, A. P. et al.: Is there a relationship between clozapine and obsessive-compulsive disorder?: a retrospective chart review. Compr. Psychiatry, 36: 267–270, 1995.
9) Khullar, A., Chue, P., Tibbo, P.: Quetiapine and obsessive-compulsive symptoms (OCS): case report and review of atypical antipsychotic-induced OCS. J. Psychiatry Neurosci., 26: 55–59, 2001.
10) Kopala, L., Honer, W. G.: Risperidone, serotonergic mechanisms, and obsessive-compulsive symptoms in schizophrenia [letter]. Am. J. Psychiatry, 151: 1714–1715, 1994.
11) Lykouras, L., Alevizos, B., Michalopoulou, P. et al.: Obsessive-compulsive symptoms induced by atypical antipsychotics. A review of the reported case. Prog. Neuropsychopharmacol. Biol. Psychiatry, 27(3): 333–346, 2003.
12) Morrison, D., Clark, D., Goldfarb, E. et al.: Worsening of obsessive-compulsive symptoms following treatment with olanzapine [letter]. Am. J. Psychiatry, 155: 855, 1998.
13) Mottard, J-P., de la Sablonniere, J-F.: Olanzapine-induced obsessive-compulsive disorder [letter]. Am. J. Psychiatry, 156: 799–800, 1999.
14) Patel, B., Tandon, R.: Development of obsessive-compulsive symptoms during clozapine treatment [letter]. Am. J. Psychiatry, 150: 836, 1993.
15) Patil, V. J.: Development of transient obsessive-compulsive symptoms during treatment with clozapine [letter]. Am. J. Psychiatry, 149: 272, 1992.
16) Rahman, M. S., Grace, J. J., Pato, M. T. et al.: Sertraline in the treatment of clozapine-induced obsessive-compulsive behavior [letter]. Am. J. Psychiatry, 155: 1629–1630, 1998.
17) Remington, G., Adams, M.: Risperidone and obsessive-compulsive symptoms. J. Clin. Psychopharmacol., 14: 358–359, 1994.
18) Sareen, J., Kirshner, A., Lander, M. et al.: Do antipsychotics ameliorate or exacerbate obsessive compulsive disorder symptoms? A systematic review. J. Affect. Disord., 82: 167–174, 2004.

特集
抗精神病薬の現在—作用機序・効果・副作用—
臨床精神薬理 9：423-429, 2006

抗精神病薬による注目すべき有害事象

——非定型抗精神病薬を中心に——

須貝拓朗* 澤村一司* 染矢俊幸*

抄録：1950年代から我が国の統合失調症治療に抗精神病薬が用いられるようになりおよそ半世紀が経つ。抗精神病薬による治療が与えた恩恵には計り知れないものがあるが，一方でその背景にある様々な副作用は治療上ある程度仕方のないものとして見過ごされてきたことも事実である。近年薬物療法の主流となっている非定型抗精神病薬は定型抗精神病薬と比較し，錐体外路症状などの副作用は少ないものの，体重増加，糖脂質代謝異常といった放置すれば糖尿病などの様々な生活習慣病をきたし得る副作用が問題となっている。また致死的な不整脈を惹起するQT延長や性機能異常を生じる高プロラクチン血症なども以前に増して関心がもたれるようになってきている。本稿では，非定型抗精神病薬を中心に注目すべき副作用をいくつか取り上げ，これまでの知見をもとに概説した。

臨床精神薬理 9：423-429, 2006

Key words：*atypical antipsychotics, weight gain, diabetes mellitus, QT prolongation, hyperprolactinemia*

はじめに

Chlorpromazineやreserpineといった抗精神病薬が我が国の統合失調症治療に用いられるようになったのは1955年からであり，現在ではその種類も多岐にわたっている。抗精神病薬が統合失調症治療に与えた恩恵は計り知れないものがあるが，一方でその背景にある様々な副作用は治療上ある程度仕方のないものとして見過ごされてきたことも事実である。定型抗精神病薬で高頻度に認められる過鎮静や錐体外路症状などの副作用は身体的苦痛および精神的苦痛を伴うだけでなく，患者のQOLを低下させ，社会復帰を遅らせる一因となっている。また日本独自の薬物療法とも言える多剤併用療法は，出現した副作用の原因薬剤同定を困難とするだけでなく，薬物間相互作用による副作用なども惹起する可能性があるために決して推奨されるべきものではない。

近年相次いで開発された非定型抗精神病薬は定型抗精神病薬と比較して，錐体外路症状などの副作用が少なく，さらに臨床効果も定型抗精神病薬と同等以上であることが明らかとなった[16]。しかし一方で，非定型抗精神病薬においては体重増加，糖脂質代謝異常といった，放置すれば糖尿病などの様々な生活習慣病をきたし得る副作用が問題となっている。日本ではolanzapineやquetiapineによる耐糖能異常が重篤なケトアシドーシスを引き起こし，それに伴う死亡例も報告され，現在，糖尿病の既往がある患者への使用が禁忌となっている[17]。この他にもかねてから抗精神病薬治療上の問題となってきたQT延長などの致死的

Notable adverse events caused by antipsychotics: A focus on the atypical antipsychotics.

*新潟大学大学院医歯学総合研究科精神医学分野
〔〒951-8510 新潟県新潟市旭町通一番町757〕
Takuro Sugai, Kazushi Sawamura, Toshiyuki Someya: Department of Psychiatry, Niigata University Graduate School of Medical and Dental Science. 757, Asahimachidori-ichibancho, Niigata, 951-8510, Japan.

な不整脈についても関心がもたれている。

本稿では，現在我が国で発売されている非定型抗精神病薬（risperidone, olanzapine, quetiapine, perospirone）を中心に注目すべき副作用をいくつか取り上げ，各々の副作用についてこれまでの知見をもとに概説する。

Ⅰ．体重増加

体重の増加は糖尿病や心血管系異常などのリスクを高め，さらには患者の服薬コンプライアンス低下につながる。以前から定型抗精神病薬が誘発する体重増加について報告されていたが，非定型抗精神病薬においては薬剤ごとに体重増加の程度に違いがあることが明らかになってきた[5,36]。

Wetterling らは非定型抗精神病薬の体重増加について検討している。彼らによると，olanzapine は2.3kg，zotepine 2.3kg，quetiapine 1.8kg，clozapine 1.7kg/月の体重増加を示し，risperidone では1.0kg/月と緩やかな増加を示したという。また，とくに治療開始後12週間における体重増加が顕著であったと報告している[42]。Allison らは抗精神病薬投与後の体重変化に関する81の二重盲検試験のメタ解析において，10週後の体重変化は clozapine で4.45kg，olanzapine 4.15kg，sertindole 2.92 kg，risperidone 2.10 kg，ziprasidone 0.04kg であったと報告している。一方，定型薬では thioridazine で3.19kg の体重増加が認められたが，逆に molindone では0.39kg の体重減少が認められたという[1]。また olanzapine に関しては，治療開始１年後の平均体重増加量は4.3kg であり，全体の28.3％が５kg～12.5kg の体重増加を認めたとの報告もある[19]。

体重増加の発現には多因子が関わっており，複雑な作用機序が関与していると考えられ，その促進因子としては治療前 Body Mass Index（BMI）が低値であることや非白人種であることなどが報告されているが[4]，詳細は不明である。しかし前述のように，短期間に急激な体重増加を示す症例も少なくない。また体重増加は薬物治療早期に認められることが多く[19]，こうした症例に対しては十分な注意が必要である。糖尿病発生のリスクも考慮した上で，体重コントロールが困難な症例については早期に体重増加のリスクが少ないとされる薬剤へ変更することが望ましい。

Ⅱ．耐糖能異常

糖尿病は一般人口においても頻度が高く，我が国では現在厚生労働省がその対策に最も力を入れている疾患の１つである。特に２型糖尿病は統合失調症患者に高率に認められることが分かっており，統合失調症と２型糖尿病との間に何らかの関連があることがうかがわれる[29]。これまでの報告で非定型抗精神病薬内服中に糖尿病を合併するリスクファクターとして男性，非白人種，中年，lithium の併用などが指摘されている[28]。非定型抗精神病薬の投薬開始後に出現した耐糖能異常が投薬中止後に消失したという症例[10,12]や非定型抗精神病薬の再投与で耐糖能異常が再度生じた症例[23]，また糖尿病を合併した患者のほとんどが家族歴を有していないという報告[28]がある。このような症例では抗精神病薬の影響で体重増加をきたし，その結果，糖尿病が発症した可能性も考えられるが，一方では投薬前後に肥満のない患者においても糖尿病の発症が認められたという報告もあり[34]，耐糖能異常の発現に対し薬剤の直接的な影響が大きい可能性が示唆される。

耐糖能異常に関する報告は clozapine，olanzapine に集中している。Goldstein らは olanzapine 内服中に糖尿病を合併した７症例について報告しており，体重増加をきたした症例は４名，さらに糖尿病性ケトアシドーシスを認めたものは２名であったという[12]。Meyer らは olanzapine 内服群と risperidone 内服群の２群間で投与１年後の体重，血清脂質，血糖値を比較したところ，olanzapine 内服群は risperidone 内服群に比べて，体重では有意差はなかったが血清脂質と血糖値が有意に高かったと報告している[26]。また Gianfrancesco らによれば，無投薬群と比較して clozapine，olanzapine 内服患者では糖尿病の有病率が高かったが，risperidone 内服群では有意差が認められなかったとしている[11]。以上のことから olanzapine や clozapine を使用する際には，定期

的な血糖モニタリングなどによるフォローアップが必要である。

Ⅲ．脂質代謝異常

抗精神病薬による高脂血症の合併についてはいまだ明確な見解が示されていないが，非定型抗精神病薬治療中の高脂血症の発現に関する報告は徐々に蓄積されている。

Sheitman らは olanzapine 内服患者の中性脂肪（TG）値が投与開始から約16週間で平均70mg/dl上昇していたと報告している[35]。Osser らは25名の olanzapine 内服患者の体重と TG 値の経時的変化について検討を行った。彼らは，体重および TG が投与開始12週時にはともに有意な上昇を示し，両者の間に強い相関が示唆されたと報告している[31]。また，Meyer らの報告では olanzapine または quetiapine を投与していた14症例に600mg/dl を超える重度の高 TG 血症を生じ，このうち9症例は投与開始8ヵ月以内に高 TG 血症をきたしていたという。しかしその時点での体重増加はわずかで，糖尿病を合併した患者も4例のみであったと報告している[27]。Clozapine についても Spivak らが clozapine 内服中の患者で1年後の TG 値が有意に上昇したのに対して，定型薬を内服している患者では上昇がみられなかったと報告している[37]。さらに Lindenmayer らは，二重盲検法で haloperidol，clozapine，olanzapine，risperidone を内服している患者の総コレステロール（TC）値を14週間追跡し，clozapine 群と olanzapine 群では8週後に TC 値の有意な上昇を認め，haloperidol 群と risperidone 群では14週後も TC 値の有意な上昇はみられなかったと報告している[22]。これらの報告は非定型抗精神病薬投与中の統合失調症患者において，高脂血症が肥満や糖尿病の結果として二次的に発症するだけでなく，非定型抗精神病薬の脂質代謝における直接的な影響により生じる可能性を示唆している。

抗精神病薬内服中に合併する高脂血症に対しては，高脂血症薬による薬物療法はもちろんのこと，脂質代謝異常のリスクが高いと考えられる olanzapine や clozapine などの使用には十分な注意が必要である。また生活習慣病という側面からも規則的な生活リズムを保つことや適度な運動を習慣づけるなど，日常生活レベルでの改善を心がけることが重要である。

Ⅳ．QT 時間延長

非定型抗精神病薬が開発される以前より，抗精神病薬内服中の心電図変化や突然死は指摘されてきた。QT 時間の延長は torsade de points（TDP）と呼ばれる致死的な発作性心室頻拍の特殊型をはじめとした心室性不整脈を生じる危険性を増大させる。また，これまでに thioridazine や chlorpromazine などの定型抗精神病薬は QT 時間を延長させることが報告されている[33]。

Czekalla らは抗精神病薬各薬剤について QT 時間の延長や，TDP 発生の危険性を比較検討した[7]。定型抗精神病薬の中では thioridazine および droperidol が最も QT 時間を延長させ，次いで chlorpromazine や pimozide が中等度の QT 時間延長を示した。一方，最も QT 時間延長に対し影響が少なかったものは haloperidol であり，平均の QT 時間変化は＋4.0～＋7.1ms であった。非定型抗精神病薬では sertindole が最も QT 時間を延長させ，ziprasidone，quetiapine，risperidone の順で続いていた。最も影響が少ないものは olanzapine で平均－4.9～＋6.8ms であった。また，Reilly らは QT 延長の危険性が抗精神病薬の用量増加に伴い高くなることを報告し，オッズ比で比較した場合，chlorpromazine 換算で1,000mg 以下の群は1.4，1,001mg～2,000mg の群では5.4，2,001mg 以上の群では8.2倍にもそのリスクが高くなるとしている[33]。

抗精神病薬使用に伴う QT 延長には，致死的な不整脈または心不全をきたす可能性がある。Thioridazine あるいは sertindole など，リスクの高い薬剤を使用する場合や，高用量の抗精神病薬を使用せざるを得ない場合には定期的に心電図をモニタリングすることが必要であろう。加えて QT 時間を延長させるその他のリスクファクターとしては，加齢や甲状腺機能低下，徐脈，三環系抗うつ薬の使用，電解質異常などが報告されており[39]，

このような状況下においてはさらに注意して薬剤を選択する必要がある。またQT時間が500msを超えるとTDP発生のリスクが高くなるという報告もあり[9]，一般的にQT時間が450ms～500ms以上の延長を示す症例では早急に薬剤の変更，または中止を考慮すべきである。

V．高プロラクチン血症

高プロラクチン（PRL）血症はドーパミンD_2受容体遮断によって起こると考えられており，女性では無月経，無排卵，性欲低下や乳汁分泌，男性ではインポテンツなどの性機能障害を引き起こす[41]。長期間遷延することによりエストロゲンやテストステロン濃度の低下をまねき，その結果骨粗鬆症や心血管系障害などを引き起こすとされている[14]。また精神症状や認知機能にも影響を及ぼすという報告もあり[25]，精神科領域においては注目すべき副作用の1つである。

定型抗精神病薬と非定型抗精神病薬について比較した報告がいくつかある。Davidらはhaloperidol，olanzapine，risperidoneを用いて二重盲検試験を行い，risperidone内服群ではhaloperidolおよびolanzapine内服群にくらべて有意な血中PRL濃度上昇を認めたと報告している[8]。またKearnsらはrisperidoneの使用により男女ほぼ全症例において，男性では37.3±23.9ng/dl，女性で125.0±56.6ng/dlのPRL値上昇を認めたとしている[16]。Olanzapineについては定型抗精神病薬に比し，PRL値の上昇が軽度であることが分かっており[40]，Crawfordらはolanzapine内服群はhaloperidol内服群に比し，PRL濃度の上昇率が2分の1から3分の1程度であり，6週目にはプラセボと比較して有意差が認められなかったと報告している[6]。一方，clozapineやquetiapineではほとんどPRL濃度を上昇させないといった報告が多い。Arvanitisらはquetiapine，haloperidol，プラセボ内服群においてPRL濃度の変化を比較したところ，haloperidol群では治療前と比較して有意にPRL濃度が上昇していたが，quetiapine群ではプラセボ群と同様に有意なPRL濃度変化は認められなかったと報告している[2]。またperospironeについては用量依存性にPRL濃度の上昇を認め，高PRL血症の発生率が27.5%であったという報告がある[24]。

抗精神病薬による高PRL血症に対しては，原因薬剤の減量・中止・変更が第一に考えられるが，実際の臨床現場では，精神病症状の再燃が危惧されるために薬剤変更が行われることが多い。しかし無月経や乳汁分泌などの症状は心理的には問題となるものの，身体的な苦痛は目立たないことが多いため，患者に対し十分なインフォームド・コンセントを行った上で，やむを得ず統合失調症の治療を優先させることもある。症状が顕著で患者の苦痛が大きい場合には薬物療法としてbromocriptineを投与することもあるが，精神病症状の悪化や錐体外路症状を引き起こす可能性があるため慎重に投与する必要がある。

VI．錐体外路症状/遅発性ジスキネジア

振戦，固縮，無動を主とした錐体外路症状（Extrapyramidal Symptoms：EPS）は抗精神病薬により脳内のドーパミンD_2受容体が遮断されることによって投薬開始数日後から発生することが多いとされる[42]。非定型抗精神病薬が開発されてからはその頻度こそ少なくなったものの，現在も薬物療法中断の最も多い理由の1つである。米国食品医薬品局（Food and Drug Administration）による報告では，risperidoneは10mg/日以下の投与量ではEPSの発症率は17%であり，プラセボ投与群の発症率15%とほぼ同等である。しかし，用量依存性を認め，16mg/日では33%まで上昇するとしている。またolanzapineにおいても10mg/日で25%，15mg/日で33%と用量依存性が認められ[38]，これらのことは非定型抗精神病薬によるEPSの発症率が定型抗精神病薬に比して低いものの，用量依存性が存在し，高用量ではEPS発症のリスクが高まることを示唆している。Risperidoneとhaloperidolの比較試験では，risperidoneが低用量（1～4mg/日）の場合EPSの発症率は低いが，高用量（16mg/日）になるとhaloperidolと同等にEPSが出現するという報告がある[32]。Leuchtらはrisperidone，olanza-

pine, quetiapine, haloperidol 間の EPS 発症頻度についてメタ解析を行い，非定型抗精神病薬は定型抗精神病薬に比して EPS 発症のリスクは低いが，非定型抗精神病薬の中でも risperidone に関してはやや高くなることを報告している[20]。また quetiapine に関しては risperidone との比較試験において，EPS 治療に使用した抗コリン薬投与の頻度が有意に少なかったという報告がある[30]。さらに quetiapine では EPS 出現に関して用量依存性がなく，高用量（750mg/日）においても有意な EPS 発症率の上昇は認められなかったとする報告もある[2]。これらのことは，quetiapine においては EPS 発症のリスクがきわめて低い可能性を示唆している。

遅発性ジスキネジア（Tardive Dyskinesia：TD）は，EPS の中ではアカシジアと並び，最も患者に苦痛を感じさせる副作用であることが知られている[15]。Guthrie らによれば定型抗精神病薬による TD の発症率は約 5 %であり，非定型抗精神病薬においては 1 %以下であるとされる[13]。しかし非定型抗精神病薬の中でも発症のリスクには違いがある。Lieberman らの報告によれば risperidone や olanzapine は用量依存性に EPS 発症のリスクが高まり，TD 発症のリスクも高くなるが，その一方で clozapine は TD 発症のリスクが非常に低いとされている[21]。また quetiapine に関しては，TD の発症率が0.4%と低率であるという報告もある[20]。

EPS に関しては抗コリン薬の併用または原因薬剤の減量，中止，変更が原則であるが，精神疾患の治療上継続を余儀なくされることも少なくない。各非定型抗精神病薬の特徴を十分に理解し，慎重な薬剤選択，用量の設定を行うことが重要であると思われる。

おわりに

以上，非定型抗精神病薬を中心として抗精神病薬によりもたらされる注目すべき有害事象について概説した。特に代謝系の異常については以前から注目されてきたものの，現在本邦で使用されている非定型抗精神病薬の 4 剤中 2 剤が糖尿病の既往または糖尿病患者において禁忌とされ，狭い範囲での薬剤選択を強いられている現状もあり，今後の大きな課題である。また日本独自の薬物療法とも言える多剤併用療法は，副作用の予測を困難とし，新たな薬物間相互作用による副作用を惹起する可能性もあり，近年ではそのあり方が疑問視されてきている。本来，副作用の出現を防ぐ最大の予防策は，まず多剤および大量療法を行わないことであるといっても過言ではないだろう。我々臨床医は，常に副作用に関する最新の知見に目を配りつつ治療に従事しなければならない。

文　献

1）Allison, D. B., Mentore, J. L., Heo, M. et al.: Antipsychotic-induced weight gain: a comprehensive research synthesis. Am. J. Psychiatry, 156(11): 1686–1696, 1999.

2）Arvanitis, L. A., Miller, B. G.: Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. Biol. Psychiatry, 42(4): 233–246, 1997.

3）Baldessarini, R. J.: Drugs and the treatment of Psychiatric disorders. In: The Pharmacological Basis of Therapeutics, 8 th edition(ed. by Gilman, A. G., Rall, T. W., Nics, A. S. et al.), pp. 383–435, Pergamon Press, New York, 1990.

4）Basson, B. R., Kinon, B. J., Taylor, C. C. et al.: Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. J. Clin. Psychiatry, 62(4): 231–238, 2001.

5）Conley, R. R., Mahmoud, R.: A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am. J. Psychiatry, 158(5): 765–774, 2001.

6）Crawford, A. M., Beasley, C. M. Jr., Tollefson, G. D.: The acute and long-term effect of olanzapine compared with placebo and haloperidol on serum prolactin concentrations. Schizophr. Res., 26 (1): 41–54, 1997.

7）Czekalla, J., Kollack-Walker, S., Beasley, C. M. Jr.: Cardiac safety parameters of olanzapine: comparison with other atypical and typical antipsychotics. J. Clin. Psychiatry, 62 (Suppl. 2): 35–40, 2001.

8) David, S. R., Taylor, C. C., Kinon, B. J. et al. : The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. Clin. Ther., 22(9) : 1085–1096, 2000.
9) Garson, A. Jr. : How to measure the QT interval —what is normal? Am. J. Cardiol., 72(6) : 14B–16 B, 1993.
10) Gatta, B., Rigalleau, V., Gin, H. : Diabetic ketoacidosis with olanzapine treatment. Diabetes Care, 22(6) : 1002–1003, 1999.
11) Gianfrancesco, F. D., Grogg, A. L., Mahmoud, R. A. et al. : Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes : findings from a large health plan database. J. Clin. Psychiatry, 63(10) : 920–930, 2002.
12) Goldstein, L. E., Sporn, J., Brown, S. et al. : New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics, 40(5) : 438–443, 1999.
13) Guthrie, S. K. : Clinical issues associated with maintenance treatment of patients with schizophrenia. Am. J. Health Syst. Pharm., 59(17 Suppl. 5) : S19–24, 2002.
14) Halbreich, U., Rojansky, N., Palter, S. et al. : Decreased bone mineral density in medicated psychiatric patients. Psychosom. Med., 57(5) : 485–491, 1995.
15) Kane, J. M., Woerner, M., Borenstein, M. et al. : Integrating incidence and prevalence of tardive dyskinesia. Psychopharmacol. Bull., 22(1) : 254–258, 1986.
16) Kearns, A. E., Goff, D. C., Hayden, D. L. et al. : Risperidone-associated hyperprolactinemia. Endocr. Pract., 6(6) : 425–429, 2000.
17) Koller, E. A., Doraiswamy, P. M. : Olanzapine-Associated Diabetes Mellitus. Pharmacotherapy, 22(7) : 841–852, 2002.
18) 工藤 喬, 武田雅俊 : 短期効果の徹底比較—非定型抗精神病薬を用いた急性期治療. 臨床精神薬理, 5 : 155–165, 2002.
19) 久米明人, 栗林和彦, 田中洋子 : 日本の精神分裂病患者における olanzapine 治療と体重変化. 臨床精神薬理, 4 : 1441–1458, 2001.
20) Leucht, S., Pitschel-Walz, G., Abraham, D. et al. : Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. Schizophr. Res., 35(1) : 51–68, 1999.
21) Lieberman, J., Kane, J., Johns, C. et al. : Clozapine : clinical evidence of novel effects. Clin. Neuropharmacol., 9 : 140–141, 1986.
22) Lindenmayer, J. P., Czobor, P., Volavka, J. et al. : Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. Am. J. Psychiatry, 160 (2) : 290–296, 2003.
23) Luna , B., Feinglos, M. N. : Drug-induced hyperglycemia. JAMA, 286(16) : 1945–1948, 2001.
24) 松原良次, 平林良登, 成田 元他 : 新規抗精神病薬塩酸 perospirone 細粒剤の精神分裂病に対する臨床試験. Kiso to Rinsyo, 31 : 2231–2251, 1997.
25) McEwen, B. S., Alves, S. E., Bulloch, K. et al. : Ovarian steroids and the brain : implications for cognition and aging. Neurology, 48(5 Suppl. 7) : S8–15, 1997.
26) Meyer, J. M. : A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients : metabolic outcomes after 1 year. J. Clin. Psychiatry, 63(5) : 425–433, 2002.
27) Meyer, J. M. : Novel antipsychotics and severe hyperlipidemia. J. Clin. Psychopharmacol., 21 (4) : 369–374, 2001.
28) Mir, S., Taylor, D. : Atypical antipsychotics and hyperglycaemia. Int. Clin. Psychopharmacol., 16 (2) : 63–73, 2001.
29) Mukherjee, S., Decina, P., Bocola, V. et al. : Diabetes mellitus in schizophrenic patients. Compr. Psychiatry, 37(1) : 68–73, 1996.
30) Mullen, J., Jibson, M. D., Sweitzer, D. et al. : A comparison of the relative safety, efficacy, and tolerability of quetiapine and risperidone in outpatients with schizophrenia and other psychotic disorders : the quetiapine experience with safety and tolerability (QUEST) study. Clin. Ther., 23 (11) : 1839–1854, 2001.
31) Osser, D. N., Najarian, D. M., Dufresne, R. L. et al. : Olanzapine increases weight and serum triglyceride levels. J. Clin. Psychiatry, 60(11) : 767–770, 1999.
32) Peuskens, J. : Risperidone in the treatment of patients with chronic schizophrenia : a multinational, multi-centre, double-blind, parallel-group study versus haloperidol. Br. J. Psychia-

try, 166(6) : 712–726, 1995.
33) Reilly, J. G., Ayis, S. A., Ferrier, I. N. et al. : QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet, 355 (9209) : 1048–1052, 2000.
34) Seaburg, H. L., McLendon, B. M., Doraiswamy, P. M. et al. : Olanzapine-associated severe hyperglycemia, ketonuria, and acidosis : case report and review of literature. Pharmacotherapy, 21 (11) : 1448–1454, 2001.
35) Sheitman, B. B., Bird, P. M., Binz, W. et al. : Olanzapine-induced elevation of plasma triglyceride levels. Am. J. Psychiatry, 156(9) : 1471–1472, 1999.
36) Simpson, M. M., Goetz, R. R., Devlin, M. J. et al. : Weight gain and antipsychotic medication : differences between antipsychotic-free and treatment periods. J. Clin. Psychiatry, 62(9) : 694–700, 2001.
37) Spivak, B., Roitman, S., Vered, Y. et al. : Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine. Clin. Neuropharmacol., 21(4) : 245–250, 1998.
38) Sussman, N. : Choosing an atypical antipsychotic. Int. Clin. Psychopharmacol., 17 (Suppl. 3) : S29–33, 2002.
39) Tan, H. L., Hou, C. J., Lauer, M. R. et al. : Electrophysiologic mechanisms of the long QT interval syndromes and torsade de pointes. Ann. Intern. Med., 122(9) : 701–714, 1995.
40) Tollefson, G. D., Beasley, C. M. Jr., Tran, P. V. et al. : Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders : results of an international collaborative trial. Am. J. Psychiatry, 154 (4) : 457–465, 1997.
41) Vance, M. L. : New directions in the treatment of hyperprolactinemia. Endocrinologist, 7 : 153–159, 1997.
42) Wetterling, T. : Bodyweight gain with atypical antipsychotics. A comparative review. Drug Saf., 24(1) : 59–73, 2001.
43) Zyprexa. [package insert]. Eli Lilly and Company, Indianapolis Ind, 1999.

■ お詫びと訂正 ■

本誌第8巻12号，2130ページ所収の Fig. 7について誤りがありました。
お詫び申し上げますとともに，下記のように訂正させていただきます。

Fig. 7の引用： 白川 治：薬物療法の実際. Clin. Neuroscience, 22(2) : 206, 2004.

編集部

特集
抗うつ薬の用量：その決め方と変え方
臨床精神薬理 9：593-599, 2006

抗うつ薬血中濃度の今日的意義

福井直樹* 染矢俊幸*

抄録：うつ病の治療は抗うつ薬による薬物治療が主体をなしているが，抗うつ薬の選択や投与量については科学的根拠が十分に得られていないのが現状である。実際の臨床では，精神症状の改善や副作用を臨床的に評価することによって，薬物の用量の調整を行い，またその薬物を継続するか他剤に変更するかなどの判断を行っている。しかし，同じ薬剤で同じ投与量であっても血中濃度は個人間で非常に大きなばらつきがあるので，投与量のみによって適切な治療計画を立てることは困難であり，客観的な指標である薬物血中モニタリング（TDM）を利用して治療計画を立てることが望まれる。三環系抗うつ薬（TCA）においてはTDMに関する研究が蓄積されその有用性が確立されているが，近年第一選択薬となっている選択的セロトニン再取り込み阻害薬（SSRI）におけるTDMの意義は確立しておらず，臨床レベルで利用されるには至っていない。

臨床精神薬理 9：593-599, 2006

Key words：*antidepressants, TCA, SSRI, blood concentration, therapeutic drug monitoring (TDM)*

はじめに

精神科薬物治療では，向精神薬による精神症状の改善や副作用を臨床的に評価することによって，薬物の用量の調整を行い，またその薬物を継続するか他剤に変更するかなどの判断を行っている。しかし，本稿でも示すように，同じ薬剤で同じ投与量であっても血中濃度は個人間で非常に大きなばらつきがあるために，投与量のみによって適切な治療計画を立てることは困難であり，客観的な指標である薬物血中モニタリング（TDM）を利用して治療計画を立てることが望まれる。

従来からうつ病の治療に使用されてきた三環系抗うつ薬（TCA）においては，TDMに関する研究が蓄積されその有用性が確立されている。一方で，最近は抗うつ薬における第一選択薬は選択的セロトニン再取り込み阻害薬（SSRI）となっているが，SSRIにおけるTDMの意義は確立しておらず臨床レベルで利用されるには至っていない。

本稿では，個人間で血中濃度のばらつきを引き起こす要因，およびSSRIにおけるTDM実用化に向けて蓄積されている研究などを中心に概説する。

Ⅰ．抗うつ薬血中濃度の個人間におけるばらつき

薬に対する反応には大きな個体差があることが古くより知られていたが，遺伝的な素因の差と環境因子の差によると考えられていた。Alexander-

Current status of therapeutic drug monitoring in antidepressant drugs.

*新潟大学大学院医歯学総合研究科精神医学分野
〔〒951-8510 新潟市旭町通一番町757〕
Naoki Fukui, Toshiyuki Someya: Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences. 757, Asahimachidori-ichibancho, Niigata, 951-8510, Japan.