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Adverse Reaction - Prescribing Cascade

Reproductive Toxicity of Paroxetine

MED CHECK

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Information Sharing to Prevent Adverse Reactions

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On 12 June 2025, a passenger aircraft crashed in western India, claiming the lives of 241 of the 242 people on board. Tragic events like this can easily give the impression that air travel is inherently dangerous. However, the actual incidence of accidents in aviation is considered to be significantly lower compared to other modes of transport. A key reason is the industry's commitment to safety. Thorough preventive strategies are formulated by the accident investigation board, and they are shared globally across airlines.

In healthcare, similar efforts to share errors and incidents are also made. Yet, as privatisation and deregulation progress, economic pressures to avoid financial losses can undermine these efforts. While the concept of "patient-centred care" has long been promoted, the growing emphasis on profitability risks driving a one-size-fits-all approach to medicine, which may not reflect what individual patients truly need. For example, clinical pathways, which aim to standardise care after hospitalisation, can help reduce errors and shorten hospital stays. However, when patients show unexpected responses—known as variances—if the system is designed to minimise effort required to address them, it may result in the mere imposition of standardised care, increasing the risk of adverse reactions.

In Japan, patients often visit multiple specialists for different symptoms, with each department prescribing medications independently. As a result, the total volume of prescriptions tends to increase over time. Currently, no single department or clinician is clearly responsible for overseeing a patient's full medication profile. Even leftover medication surveys are rarely conducted systematically. Once a prescription has been dispensed and reviewed by a pharmacist, responsibility for whether to take the prescribed medicines often shifts entirely to the patient. If the patient feels unwell after taking the medication, they may simply consult another specialist—potentially receiving more prescriptions. This can increase the risk of a prescription cascade, in which one adverse effect leads to another.

As discussed in our previous issue, Charles Medawar once remarked that "The medicine consumers have a vital part to play." His message is highlighted once again in another article in this issue（page 45-46）, as it remains highly relevant. Without feedback from patients, safe medical care cannot be provided. Ensuring appropriate informed consent in clinical practice can help prevent the adverse reaction-prescription cascade. To achieve this, not only doctors, but also nurses, pharmacists, and other healthcare staff must be actively listening to patients. The medical professionals are required to share information with patients and make use of that information effectively.

New Series (Part 1)

From Familiar Adverse Reactions to **Adverse Reaction–Prescribing Cascade**

Translated and revised from Med Check (in Japanese) May 2025: 25 (119): p56-61.

MedCheck Editorial team

Introduction to the new series

Many of our readers may already be familiar with the term “adverse reaction” . However, in pharmaceutical guidelines, package inserts, and the media, the term “side effect” is far more commonly used. To begin this series, we present a Q&A between the non-professional editorial staff members A and B and Dr Hama, to explain the basic concepts of “adverse reactions” and “cascades” .

On the effectiveness of medicines

***Hama*:** Let me start by sharing my personal experience of when I was truly grateful for medication.

When I had a gout attack, non-steroidal anti-inflammatory drugs (NSAIDs) were incredibly helpful. In my youth, I once had a gout attack that resolved within about three hours by drinking lots of water and urinating every five minutes, so I did not require any medication. However, when I had an attack in my seventies, drinking water alone was not enough. After taking naproxen, the pain and swelling subsided smoothly. I was genuinely thankful for the medicine.

As a doctor, I’ve also seen how salbutamol inhalers work quickly for asthma patients, and I truly appreciate the value of such medication. For people with diabetes who lack insulin, insulin injections are absolutely essential.

Have you had any similar experiences?

***A*:** Yes, when I accidentally burned my finger, applying a steroid ointment really helped.

***Hama*:** Indeed, topical corticosteroids are effective when used promptly for minor burns. They can prevent the condition from worsening.

***B*:** When I must work despite a headache, I sometimes rely on painkillers.

***Hama*:** Pain is one of the most distressing symptoms. For cancer patients, opioids like morphine are also critical medicines.

***A*:** This series is titled “From Familiar Adverse Reactions to the Adverse Reaction–Prescribing Cascade”. Why did you begin by discussing the benefits of medications, and what does the term “cascade” mean in this context?

***Hama*:** MedCheck has sometimes been criticised for focusing only on negative aspects of drugs—saying they don’t work or they’re harmful. So I wanted to first emphasise that we fully understand how beneficial and important medicines are to people.

As for “cascade”, I’ll explain that in detail later, after we’ve talked about “adverse reactions”.

Adverse reaction and side effect: same or different?

***B*:** I see. By the way, the term “adverse reaction” isn’t commonly used, and most people say “side effect”. Why does MedCheck use the term “adverse reaction”?

***Hama*:** Let’s take insulin as an example. I once served on the Osaka Prefecture Adverse Drug Reaction Study Committee. When low blood sugar (hypoglycaemia) was reported as a “side effect”, doctors who had recently joined the committee often objected, saying: “Lowering blood sugar is insulin’s main effect, not a side effect.”

However, the World Health Organization (WHO) classifies hypoglycaemia as an adverse reaction.

"Adverse" means something that goes against the intended purpose of the medication, and "reaction" means the body's response.

Insulin is normally secreted as needed to help the body utilise not only sugar but also other nutrients, including protein and lipids. It influences over 100 genes to regulate overall metabolism. When the body does not need insulin, its production naturally decreases to help prevent hypoglycaemia.

The purpose of insulin therapy is to compensate for the deficiency of insulin, prevent complications, prolong life expectancy, and improve quality of life (QOL). However, when insulin is administered as a drug, it can act when it is not needed as well, leading to "hypoglycaemia". The body then releases adrenaline to raise blood sugar, which can overstimulate the heart and cause blood vessels to constrict, resulting in tissue damage. This is an extremely harmful response—a textbook example of an adverse reaction that works counter to its intended purpose[1](See **Column 1**).

While it is misleading to regard the primary action of insulin as "lowering blood glucose", the term "side effect" tends to lack the connotation of actual harm, and can therefore be misleading. This is why we have come to consider "adverse reaction" to be a more appropriate term[1]. For patients with diabetes who use glucose-lowering agents, "hypoglycaemia" is, indeed, a very familiar adverse reaction.

Everyday examples of adverse reactions

***B*:** Would feeling drowsy from hay fever medication—probably an antihistamine—be an example of a familiar adverse reaction?

***Hama*:** Absolutely.

***A*:** I sometimes get diarrhoea from chewing gum or sucking cough drops, even though they aren't medicines. I suspect that artificial sweeteners may be to blame.

***Hama*:** You've observed a pattern between your actions and symptoms, and managed to avoid severe diarrhoea. Some people aren't so fortunate and end up losing weight just from chewing gum.

***A*:** What? Did they use chewing gum as a diet aid?

***Hama*:** No, these are adverse reaction cases reported overseas. A 21-year-old woman lost 11 kg after developing chronic diarrhoea from chewing more than 12 pieces of sorbitol-containing gum a day, without realising the cause[2]. There was also a 46-year-old man who lost 20 kg[2], and a 59-year-old woman who chewed a pack of gum a day (16 to 18 pieces) and suffered from diarrhoea for a year, losing 5.6 kg as a result[3].

The physician who reported these cases finally suspected that the sorbitol in the chewing gum was the cause of the diarrhoea. After stopping the gum and confirming that the diarrhoea resolved, the cause was finally identified. However, it took considerable effort to reach that conclusion — various tests, including endoscopy, had been performed, all of which came back normal. In one of the three cases [3], infectious enteritis had been suspected at one point, and the antibiotic metronidazole was prescribed. In this case, the antibiotic was used only for a short period, so no problems arose, but if it had been used long term, it could potentially have caused new neurological complications [4,5].

***B*:** So it's important to pay close attention to changes in our own bodies.

Column 1

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) defined in 1995 the term adverse event as any unfavorable occurrence following the proper use of a drug, including those unrelated to the drug itself [22]. Among adverse events, those for which a causal relationship with the drug cannot be ruled out are defined as adverse reactions [22b].

However, Japan's regulatory authorities at the time (the Ministry of Health and Welfare) translated adverse event as "yūgai jishō" (harmful event), and have traditionally used the term "fukusayō" (side effect) to translate adverse reaction [21]. The Med Check has been using the term "gai hannō" (harmful reaction) to clearly convey the meaning of adverse reaction as "unfavorable effects" [1].

***Hama*:** Exactly. If you notice the cause and stop or reduce exposure, there's no problem. But if you don't notice or misattribute the cause, a new drug may be prescribed, and the cycle of adverse reactions may begin—leading to today's topic: the "adverse reaction–prescribing cascade".

***A*:** When I had a bad cough, I took codeine to suppress it, but after just one dose I developed severe itching all over my body. The Ventolin inhaler was effective, but after only the second use, my hands started trembling badly. I felt the cough was easier to cope with than these adverse reactions, so I stopped using it. Was that the right decision?

***Hama*:** Yes, Certainly. Since the symptoms appeared after just one or two doses, it was probably easier to notice them. But if they had developed more gradually, this could have been a case of what's known as an "adverse reaction cascade". If the tremor had been misdiagnosed as Parkinson's disease, anti-Parkinson's medication might have been prescribed, potentially leading to further adverse reactions — a classic example of an adverse reaction-prescribing cascade.

What is an adverse reaction–prescribing cascade?

***B*:** So, does "cascade" mean that things happen in a sequence?

***Hama*:** Yes. The word "cascade" originally referred to a waterfall or a series of small waterfalls. Over time, it has also come to describe sequences of chemical reactions or physical events that occur one after another.

I used to use the term "adverse reaction cascade" to describe a chain where one adverse reaction leads to a new prescription, which in turn causes another adverse reaction, prompting yet another prescription [6]. Later, I learned that in Western countries, this same phenomenon is referred to as a "prescribing cascade" [7,8]. That's why, in this series, we've chosen to use the term "adverse reaction–prescribing cascade".

***B*:** Taking painkillers upset my stomach — that seems like a fairly common adverse effect. Could this also lead to an adverse reaction–prescribing cascade?

***Hama*:** It certainly can. I was once asked to provide an expert opinion in a medical malpractice case where a strong NSAID caused a gastric ulcer, which in turn led to gastric arterial rupture and shock. The patient suffered haematemesis and seizures, and ultimately died (see **Column 2**).

***A*:** That sounds like a case of inappropriate prescribing — a medical error, essentially. But can a patient still die even if the drug was used correctly?

***Hama*:** Yes. I've looked into this question — not just when adverse events result from clearly inappropriate

Column 2

Treatment for epiglottitis led to an adverse reaction cascade resulting in death [6]

At the back of the throat, there is a part called the epiglottis that covers the larynx (the vocal cord area). Acute epiglottitis is a condition where this part becomes infected and swollen. A man in his 60s developed this epiglottitis and was prescribed not only antibiotics but also corticosteroid injections and oral non-steroidal anti-inflammatory drugs (NSAIDs), specifically diclofenac. Unfortunately, such a prescription pattern is common. It should be noted that corticosteroids are necessary in cases of acute epiglottitis in infants and young children because their airways are prone to obstruction.

Three days later, the swelling of the epiglottis had subsided, but the patient developed stomach pain and passed black, tar-like stools. Black stools indicate bleeding from a gastric or duodenal ulcer. At this point, only antibiotics should have been continued, and the NSAIDs and steroids, which were causing gastrointestinal symptoms, should have been discontinued. The patient required hospitalization. However, the doctor only slightly reduced the steroid dose, added an intravenous H_2 blocker (acid suppressant), and continued the NSAIDs.

The gastric ulcer progressed, eventually causing two arteries in the stomach to rupture, resulting in shock. The patient vomited blood due to excessive use of vasopressors. Furthermore, due to inappropriate management, the patient developed seizures and ultimately died. The case went to court [6]; the first trial ruled against the plaintiff (the victim's family), but on appeal, the High Court recognized the doctor's negligence.

prescribing or management, but also when severe adverse reactions occur despite proper treatment. According to Japan's Vital Statistics, the number of accidental deaths — such as from traffic accidents — was around 36,000 in 1994 and about 44,000 in 2023.

While Japan's statistics do not specifically report deaths from adverse drug reactions, I looked into which was higher: the number of such deaths or those caused by accidents.

There's no direct data from Japan, but two reliable datasets are available overseas [10,11]. I converted the data to reflect Japan's population size [12] and estimated the number of deaths due to adverse drug reactions in Japan. Based on either dataset, it turns out that approximately 50,000 people die each year from adverse reactions (Explained briefly in the **Column 3: p30**).

This number is actually higher than the number of accidental deaths not only in 1994 but also in 2023.

***B*:** What, 50,000 deaths!? That's a shocking figure. If that's accurate, it's something the public ought to be far more aware of. We need to take this more seriously.

***Hama*:** I believe you've now got a good grasp of the basics. From here, we'll move into something more technical. I encourage you to read carefull

Delirium Induced by the Anti-Ulcer H_2 Blocker : Outcomes Hinge on Management

This first article in this series introduces two cases of delirium caused by famotidine (Gaster ®), an H_2 blocker, that was most commonly used as an anti-ulcer agent in Japan during the 1990s. Although both cases involved delirium, the outcomes diverged significantly due to differences in clinical management.

Case 1 [13]: Delirium resolved by discontinuation

An 87-year-old man was admitted with a bleeding duodenal ulcer and developed delirium while in the ICU. The delirium began two to three hours after the third intravenous dose of famotidine, administered as an anti-ulcer agent. The patient became restless, attempting to get out of bed and insistently saying he wanted to "go home," causing distress to his accompanying family.

The patient's son, a physician, was informed of the situation, and suspected famotidine-induced delirium. He requested the on-call physician to discontinue famotidine from the following day. The on-call physician initially insisted that the delirium was due to ICU syndrome ("ICU psychosis"), but ultimately agreed to stop the famotidine. Although the patient remained in the ICU the following day, the delirium symptoms had resolve. This confirmed that the delirium was caused by famotidine, not ICU syndrome.

Case 2 [13]: Continued famotidine treatment followed by fever, shock, and death

A man in his late 40s with lung cancer metastatic to bone was undergoing two types of combination chemotherapy but with no tumour reduction. For bone metastasis-related pain, he was taking sustained-release morphine, betamethasone (2 mg), and triazolam (0.25 mg) for sleep, along with combined analgesics (four ingredients, icluding isopropyl-antipyrin) as needed.

Two days before admission, he experienced intermittent left lower abdominal pain and was admitted to hospice care with suspected localized peritonitis related to intestinal lesions. In addition to antibiotics, fluids, and betamethasone (2 mg), he received intravenous famotidine (one ampoule, estimated 20 mg) diluted in 20 ml saline, administered twice daily, from the late afternoon of admission.

During the daytime on the day of admission, prior to famotidine injection, his responses were clear. However, by the following afternoon, he exhibited delirium, including attempts to remove his urinary

catheter.

The attending physician suspected morphine-induced delirium and reduced the dose from 150 mg to 90 mg per day, but symptoms did not improve and actually worsened. At admission, serum creatinine was 1.86 mg/dL (creatinine clearance 40.8 mL/min). Delirium appeared shortly after famotidine injection, lessened within a few hours, but recurred with subsequent doses.

On day 5, haloperidol 5 mg was added intravenously (mixed with 20 mL saline) for presumed delirium of unknown cause. However, administration of both famotidine and haloperidol triggered sudden agitation that subsided within hours, only to recur with the next injection, a pattern noted by family members.

Following haloperidol initiation, new symptoms appeared, including upward eye deviation (oculogyric crisis), teeth clenching as dystonic reactions, and aimless wandering (akathisia). Subsequently, the patient gradually became less mobile. In the afternoon of day 6, he developed a fever of 38.2 ℃. In response, a 50 mg diclofenac suppository was administered, after which he experienced hypotension and respiratory deterioration. He died in the early hours of day 7.

Commentary on case 2

①Famotidine was unnecessary: Famotidine is indicated for treatment and prevention of gastric and duodenal ulcers but is not indicated for small or large bowel conditions, making its use here unnecessary.

②Dosage and administration were inappropriate: A creatinine clearance of 40.8 ml/min corresponds to moderate renal impairment; therefore, the maximum daily dose of famotidine should be 20 mg. Intravenous injection over a short period (rather than infusion) led to rapid peak blood levels, rendering administration unsuitable even if indicated.

③The cause was predictable: Delirium worsening after each injection and improving before the next was noticeable to the family. Careful observation should have led to suspecting famotidine, its discontinuation, and resolution.

④Information was available in the package insert: Mental disturbances and seizures caused by H_2 blockers were documented in official information [14–15] and the package insert [16], including guidance on dosage adjustment for renal impairment [17,18]. The package insert had also been revised accordingly [19].

⑤Antipsychotic therapy began without stopping famotidine: Rather than stopping the offending drug (famotidine), the clinician prescribed haloperidol, a strong neuroleptic (antipsychotic) medication, as symptomatic treatment for delirium.

⑥A series of extrapyramidal symptoms caused by haloperidol: Symptoms such as dystonia (oculogyric crisis, teeth clenching), akathisia (restlessness, inability to remain seated), and fever consistent with neuroleptic malignant syndrome appeared [20], yet haloperidol was not discontinued.

⑦Extrapyramidal symptoms, such as oculogyric crisis, were not recognised as adverse reactions: Neuroleptic malignant syndrome went unrecognised, and treatment with NSAIDs (diclofenac) was given, leading to shock and death.

⑧Summary: The patient developed typical delirium after starting famotidine, which was ineffective for abdominal pain of intestinal origin. However, the adverse reaction was not recognised and famotidine was continued. Symptomatic treatment with neuroleptics was administered, leading the following day to acute dystonic reactions and other extrapyramidal symptoms (akathisia and parkinsonism followed by catatonia), which were also not addressed. The condition progressed to neuroleptic malignant syndrome with associated fever, for which antipyretics were given as symptomatic treatment. This resulted in shock and subsequent death. This case exemplifies a fatal adverse reaction–prescribing cascade.

When adverse reactions are missed, unnecessary prescriptions lead to cascades

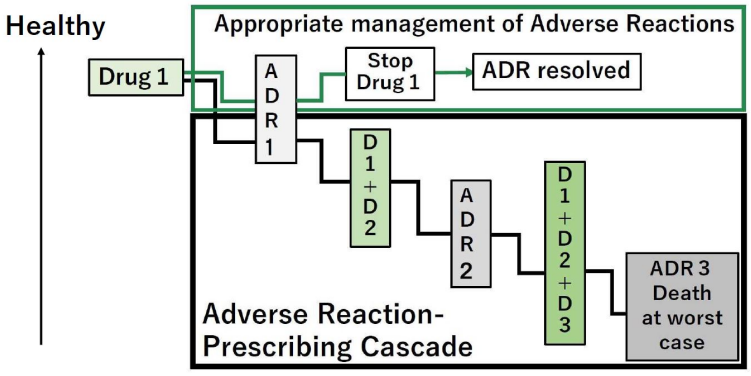
By looking at these two contrasting cases, we will explore how adverse reaction–prescribing cascades can be avoided or lead to fatal outcomes.

In **Case 1**, delirium (adverse reaction 1: **Figure**) appeared 2–3 hours after the third infusion of famotidine (drug 1). Famotidine was recognized as a cause and was promptly discontinued, and the symptoms resolved by the next day (proper management, upper part of diagram). However, had the

family not advocated for stopping the drug, the outcome could have mirrored Case 2.

In **Case 2**, delirium (adverse reaction 1) developed after starting famotidine (drug 1) but was not recognised as an adverse reaction. The physician attributed the new symptoms to delirium of unknown cause and prescribed haloperidol (drug 2) for symptomatic control (see lower part of the diagram: adverse reaction–prescribing cascade). Subsequent extrapyramidal symptoms—including dystonia, akathisia, parkinsonism, catatonia and neuroleptic malignant syndrome with fever (adverse reaction 2)—occurred; however, haloperidol was not discontinued. Instead, the antipyretic diclofenac (drug 3) was administered for the fever, which led to shock and death.

Figure：Appropriate management of Adverse Reactions and the Development of an Adverse Reaction–Prescribing Cascade



ADR: Adverse Drug Reaction, D: Drug

As seen in this case, when Adverse Reaction 1 occurs in response to Drug 1, but Drug 1 is not discontinued, a new Drug 2 was prescribed to manage Adverse Reaction 1. This lead to Adverse Reaction 2, for which Drug 3 then was prescribed, resulting in Adverse Reaction 3, and so on. This repeated cycle of adverse reactions followed by new prescriptions is known as the adverse reaction–prescribing cascade.

How to prevent harm from medications

"Drugs, being foreign to the human body, only by chance evolve therapeutic value and it is more or less inevitable that they harbor some undesirable effects. To prevent drug-induced harm, the following 4 caveats are essential; ❶ develop a drug with least possible hazard; ❷ collect as detailed information as possible about adverse reactions to the drug even after careful screening; ❸ find the safest way of drug administration based on the above-mentioned information; ❹ always be alert for unknown harms."

Above remarks were originally made by Dr Shigeichi Sunahara in a keynote lecture at the Kyoto International Conference against Drug-Induced Suffering in 1979 [30]. Dr Sunahara (1908–1988) was the first physician who conducted a randomised controlled trial (RCT) in Japan and confirmed the efficacy of anti-tuberculosis drugs. Although these remarks were made nearly half a century ago, he outlined four important precautions for safe drug use that remain relevant today.

This journal has previously published information corresponding to Dr Sunahara's points:

Regarding point ❶ , Articles in the ***New Products*** section examine the benefits and harms of substances developed and approved as medicinal products as articles for "New Products";

Regarding point ❷ , Articles in the ***Adverse reactions*** section provide information necessary to minimise adverse reactions.

Regarding point ❹ , ***Adverse reactions*** section also adress the potential for unknown adverse effects, although these are not widely known to the general public.

The new series ***"From Familiar Adverse Reactions to Adverse Reaction–Prescribing Cascades"*** can be regarded as adressing the Sunahara's point ❸ — namely, whether medicines are being used as safely as possible, based on the information currently available.

In the **Column 3** (next page), we also discussed briefly the scale of mortality and economic losses resulting from adverse drug reactions. Beyond the H_2 blockers discussed in this issue, there are many other medicines that can cause delirium. Drugs that commonly cause oedema, parkinsonisms, hypertension, or arrhythmias can lead to an adverse reaction–prescribing cascade if the initial adverse

reactions go unrecognised and additional drugs are prescribed in response.

We encourage readers to share their own clinical experiences and insights. Your contributions could serve as valuable information for others. Please feel free to send us your opinions and case examples.

Column 3

Adverse Drug Reactions Rank as the Fifth to Seventh Leading Cause of Death.

Serious ADRs account for 6.7% of hospitalized patients

A substantial number of systematic reviews on the scale of serious and fatal adverse drug reactions (ADRs) have been reported [10, 23-26]. “Serious ADRs” are defined as the sum of ADRs resulting in hospitalization and serious ADRs during hospitalization.

A systematic review of literatures published in the United States between 1966 and 1996 [10] reported that serious ADRs occurred in 6.7% of hospitalized patients. A review published between 2012 and 2021 found an average incidence of 8.3% [23]. A systematic review of elderly patients [24] found an average of 11%, while reviews of children reported an average of around 3% [25,26].

These reports exclude cases of drug overdose and inappropriate prescribing. However, a report that found 8.3 % of hospitalized patients had serious ADR [24] stated that nearly half (45%) of these were preventable. When including cases of overdose and inappropriate prescribing, ADRs accounted for 13.9% of hospitalizations - of which 71% were considered preventable [24].

ADRs rank as the fourth to seventh leading cause of death.

According to a US review [10], deaths due to ADRs occurred in 0.32% of all hospitalized patients. Applying the rates of 6.7% and 0.32% to the total number of hospitalized patients in the United States in 1994 (approximately 33 million), there were 2.22 million patients with serious ADRs and 106,000 deaths, accounting for 4.7% of all deaths. These figures correspond to the fourth to sixth leading cause of death in the United States [10].

If these figures are extrapolated to Japan’s 1994 population, the estimate would be 1.05 million serious ADRs and 50,000 deaths. This is higher than the 36,000 “deaths due to accident,” the fifth leading cause of death in Japan’s vital statistics at the time. In 2023, with a more aged population, “deaths due to accident” was 44,000 (ranking seventh), yet the estimated 50,000 ADR-related deaths would still exceed this number.

A 2007 Swedish study [11] reported that of 1,574 deaths in a certain region, 49 (3.1%) were attributed to ADRs. Among 639 hospitalised patients, 41 (6.4%) deaths were believed to be ADR-related. These proportions are roughly equivalent to the rate of ADR deaths among all deaths in the United States [10]. In Japan, with a total of 1.57 million deaths in 2022, applying the 3.1% rate would also suggest approximately 50,000 ADR-related deaths - roughly consistent with earlier estimates.

The medical costs of ADRs are enormous.

What does it mean that so many people are dying from ADRs? Although life cannot be measured in monetary terms, let’s look at the cost of treating ADRs as a benchmark.

At two teaching hospitals (each with 700 beds) in the United States, the annual cost of treating ADRs was $5.6 million (approximately ¥600 million at the exchange rate at the time) [27]. Based on this, the average cost of hospitalization due to ADRs across the United States has been estimated at $76.6 billion [28].

When applied to Japan, this would amount to estimated ¥2 trillion — equivalent to approximately 7% of Japan’s total national medical expenditure of ¥27 trillion in 1995, and approximately 27% of total drug expenditures of ¥7.3 trillion. Such a significant amount of money is being spent for treating ADRs, which in turn increases the overall strain on healthcare costs.

Preventing ADRs is a responsibility of medical professionals

Preventing avoidable drug-related harm, unnecessary hospitalizations, and needless loss of life is an important responsibility of medical professionals.

For patients who suffer directly, it is extremely important to understand that so many people are losing their lives due to adverse reactions caused by drugs that were meant to aid treatment.

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Reproductive Toxicity of Paroxetine (Paxil ®)

Focus on Withdrawal Syndrome and Persistent Pulmonary Hypertension

Translated and revised from The Informed Prescriber (in Japanese) October 2009; 24(10):125-132

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It is widely recognized that serotonin reuptake inhibitors (SRIs) cause harms to the reproductive systems including teratogenicity and loss of libidos in both female and male. However, it is less known that they cause mating failure, infertility damage to the male reproductive organ and/or withdrawal syndrome and persistent pulmonary hypertension in newborns.

The following is a Japanese article published in 2009 that analysed reproductive toxicity of the SRI based on the Summary Technical Documentation (STED) for paroxetine (Paxil ®).

STED is a summary of the application dossier for Japanese marketing authorization prepared by the pharmaceutical company which contains not only the summary reports of clinical studies but also those of preclinical studies including animal toxicity studies. They are publicly available at the website of the Pharmaceuticals and Medical Devices Agency (PMDA) for new products approved in 2000 or later and they typically exceed 700 pages.

STED of Paxil ® contains the data indicating the facts above that are poorly recognized even today. This article reported that paroxetine caused dose-dependent increase of neonatal death that may be related to the withdrawal syndrome including respiratory distress, and persistent pulmonary hypertension in human newborns. It also reported mating failure and infertility observed even when only males were exposed and organic dameges in male reproductive organ in animal toxicity studies.

Abstract

- The reproductive toxicity of paroxetine beyond its teratogenic effects, focusing particularly on neonatal toxicity was analysed and its relationship to withdrawal syndrome and persistent pulmonary hypertension was discussed.
- The most notable toxicity observed in animal studies was increased neonatal mortality. At 4.3 mg/kg, equivalent to the upper limit of the usual human dose (40 mg/day), 69.1% of neonates died within four days (compared with 11.5% in the control group). Even at 1 mg/kg, corresponding to the lower limit of the usual human dose (10 mg/day), 18.5% of neonates died within four days (compared with 6.1% in the control group). The odds ratio for neonatal death by day four was 3.49 (95% CI: 2.05–6.54, $p < 0.0001$) compared with the control group. When combined with two additional experiments (measuring 7-day mortality), where more deaths occurred in the control group, the odds ratio was 3.38 (95% CI: 2.27–5.03, $p < 0.0001$). These findings provide strong evidence that neonatal mortality in rats increases at levels equivalent to normal human doses.
- Other toxic effects observed included significant dose-dependent increases in mortality among parent rats (both male and female), failure to mate or copulate, infertility (lack of conception), miscarriage (total resorption), post-implantation fetal death, low fetal weight, and neonatal death (within 4 or 7 days). Infertility was observed even when only males were exposed. In males, reductions in sperm count and mobility, epididymal swelling and abscess, spermatoceles, and seminiferous tubule atrophy were also noted. Exposure during the organogenesis period led to a significant, dose-dependent increase in skeletal abnormalities.
- The first reported case of neonatal withdrawal syndrome in a newborn exposed to an SRI (fluoxetine) occurred in 1993, with the first case related to paroxetine reported in 1997.

- A cohort study with a control group showed that when paroxetine was used in late pregnancy, 22% of newborns developed withdrawal syndrome, primarily convulsions (compared with 5.6% in the control group). The odds ratio for respiratory distress when paroxetine was used in late pregnancy was 10.35 (95% CI: 1.27–84.67), with an adjusted odds ratio of 9.53 (95% CI: 1.14–79.3).
- A case-control study indicated that the risk of persistent pulmonary arterial hypertension could be 6.1 times higher (adjusted odds ratio) with SRIs and 25 times higher (odds ratio) with paroxetine compared with no SRI exposure.
- There is no doubt that exposure to SRIs during late pregnancy frequently results in withdrawal symptoms, including irritability and convulsions, in newborns. Withdrawal from paroxetine is associated with an increased risk of persistent pulmonary hypertension, which may hinder the natural closure of atrial or ventricular septal defects, potentially leaving these defects permanent. Additionally, animal studies have raised concrete concerns about the negative effects of paroxetine exposure on mental and neurological development.
- Paroxetine should be contraindicated not only during pregnancy but also in women capable of becoming pregnant. For those currently using paroxetine, the dose should be gradually reduced and discontinued. Package inserts and informational leaflets should explicitly state the associated risks, including an increased risk of congenital abnormalities, a 22–32% incidence of severe withdrawal symptoms, and a 25-fold higher risk of persistent pulmonary hypertension.

Key words:
neonatal mortality, mating failure, infertility, newborn withdrawal symptoms, respiratory failure, persistent pulmonary hypertension

Introduction

Healy et al. offer an in-depth report on the teratogenic effects of paroxetine (Paxil ®) [1]. However, their report does not explore in detail the associations between paroxetine and infertility, spontaneous miscarriage, preterm birth (low birth weight), neonatal withdrawal syndrome, persistent pulmonary hypertension in neonates, and organic damage in the reproductuve system in men. This report aims to supplement those gaps by presenting findings from animal studies, specifically focusing on neonatal mortality, and reviewing literature on neonatal withdrawal syndrome and persistent pulmonary hypertension in humans. This article is a condensed version of the original report published in Internet Newsletter (Web MedCheck in Japanese) No. 135. For further details, please refer to the original report at http://npojip.org (in Japanese)

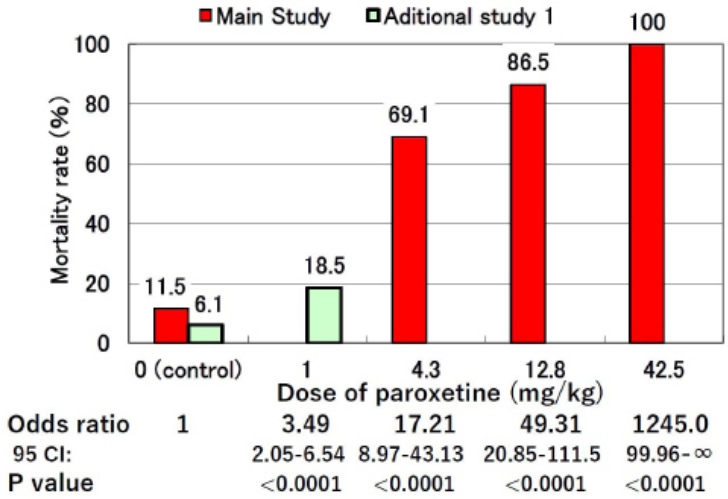
1. Animal experiment

1.1. Increased mortality rate in parent rats due to paroxetine use

There was a dose-dependent increase in mortality among the parent rats. Fertility and general reproductive function tests in the Summary Technical Documentation (STED: p153-157) were conducted on Sprague-Dawley (SD) rats (with 30 males weighing 110-155 g and 30 females 160-200 g at the start of administration). Males received paroxetine from 10 weeks prior to mating until the end of the mating period, while females were administered paroxetine from 2 weeks before mating through day 18 of gestation (in the cesarean section group) or until day 23 postpartum (in the natural pregnancy group).

In the control group, which received distilled water, no deaths were observed in either males or females. In contrast, the paroxetine-treated groups showed a significant dose-dependent increase in mortality for both sexes. (Trend analysis: p = 0.0004 for males and p =

Figure 1: Neonatal 4-day mortality rate of infants born from mothers exposed with paroxetine during pregnancy compared with control groups



Created by using the data in Table D-14 on p153-154 and Table D-15 on p155-156 of the STED for Paxil. The method for estimating the number of births and 4-day deaths required to calculate the odds ratio is described in the footnotes (calculation of "4 day mortality (M) ") of the Supplementary tables on page 43-44.

Because there are three paroxetine groups in the main study, the numerator and denominator of the control group were divided into three equal parts, one of which was used as the control group for each group to calculate the odds ratio. For a human weighing 50kg, 1(mg/kg) is equivalent to 10mg and 4.3mg/kg is equivalent to 43mg. In all paroxetine groups mortality is significantly higher compared with control group ($p<0.0001$).

0.02353 for females)

In the STED (p153-154), the cause of all observed deaths is described as "administration errors." However, given the significant results from trend analysis for both males and females and the absence of deaths in the control group, these fatalities should be considered related to paroxetine rather than to dosing errors.

1.2. Neonatal death within 4 days: significant, dose-dependent increase from the lowest dose

The primary observed toxicity was neonatal death within the first 4 days (**Figure 1**). The 4-day mortality rate was calculated as described in the foot notes of the supplementary tables. In the control group, the mortality rate was 11.5%; however, in the low-dose group (4.3 mg/kg), it increased significantly to 69.1%. A dose of 4.3 mg/kg in rats is equivalent to 43 mg/day in a 50 kg human (Note a).

Based on these findings, the NOAEL (No-Observed-Adverse-Effect Level) for fetuses and newborns was determined to be less than 4.3 mg/kg, as stated in the STED (p154) [2]. Therefore, an additional experiment (Additional Experiment 1) was conducted using an even lower dose of 1 mg/kg (approximately equivalent to 10 mg for a 50 kg human) with different rat strains (STED p155-157, Note b).

Results from both the main experiment and Additional Experiment 1 are presented in **Figure 1.** In Additional Experiment 1, the 4-day mortality rate for newborns was significantly higher in the 1 mg/kg group at 18.5%, compared with 6.1% in the control group, with an odds ratio of 3.49 (95% confidence interval 2.05, 6.54, $p < 0.0001$).

However, based on these experiments, STED stated that 1 mg/kg was deemed the NOAEL for both parent animals and the subsequent generation (fetuses and neonates). This is clearly a misinterpretation of the data.

It should be noted that in an article published in 1989 [3] about these experiments, the original main experiment was reported with control, 4.3, 13, and 43 mg/kg groups. It stated that "in all dose groups, 4-day mortalities increased ($p < 0.01$), but the additional toxicity study conducted at 1 mg/kg showed no effect."

Note a: The dose level of 4.3 mg/kg for rats corresponds approximately to a human-equivalent dose of 0.86 mg/kg when adjusted for body surface area. For a 50-kg woman, this equates to approximately 43 mg. In a comparison of blood concentrations, when male rats received a daily dose of 5 mg/kg of paroxetine for 92 to 94 days, their average blood concentration 4 hours after the final dose was 102.5 ng/mL (range: 31.6–315 ng/mL) (STED p192). It is known that when the paroxetine dose is doubled, the blood concentration can increase roughly fourfold [2]. Although no data on the daily use of 40 mg is available, we can estimate that the blood concentration is 130–240 ng/mL based on various data I mentioned in the original report. A 5 mg/kg dose in rats may be comparable to, or even lower than, a 40 mg daily dose in healthy Japanese adults. In studies where direct blood concentration comparisons are not possible, body surface area conversions may serve as an effective estimation method.

Note b: In the main experiment, SD rats were used, while in the additional experiment, Wistar FU (RORO) rats were used. The dosing schedule was as follows: In the 1 mg/kg group, males received 1 mg/kg

of paroxetine from 9 weeks before mating through the mating period. In the control group and the 50 mg/kg group, males were administered either distilled water or paroxetine for 23 weeks, followed by a 3-week rest period, after which they were mated with untreated females. Females received either distilled water or paroxetine starting 2 weeks before mating and continued until either 19 days post-conception in the cesarean group or 21 days after birth in the natural delivery group.

1.3. Results of the meta-analysis of three experiments using 1 mg/kg administration

Following Additional Experiment 1, two further experiments involving a 1 mg/kg dose were conducted, resulting in a total of three experiments at this dosage. In Additional Experiment 2 (STED p164), the control group received vehicle as inactive ingredients, and the 1 mg/kg group received paroxetine, both from the 15th day of pregnancy (late pregnancy) until the 24th day postpartum. In Additional Experiment 3, conducted to obtain approval in Japan, paroxetine or a control substance (vehicle) was administered from day 6 of gestation until day 20 postpartum. Both Additional Experiments 2 and 3 were conducted using SD rats. Using the same methodology as in Additional Experiment 1 to calculate the 4-day mortality rate, 7-day mortality rates were calculated for Additional Experiments 2 and 3, and a meta-analysis was performed on these results (shown in **Figure 2**).

The odds ratios exceeded 1.0 in all experiments. The combined odds ratio was 3.38 (95% CI: 2.27-5.03, P < 0.0001) without heterogeniety: I^2 (inconsistency) = 0%.

These findings clearly indicate a significant increase in neonatal mortality in the 1 mg/kg group.

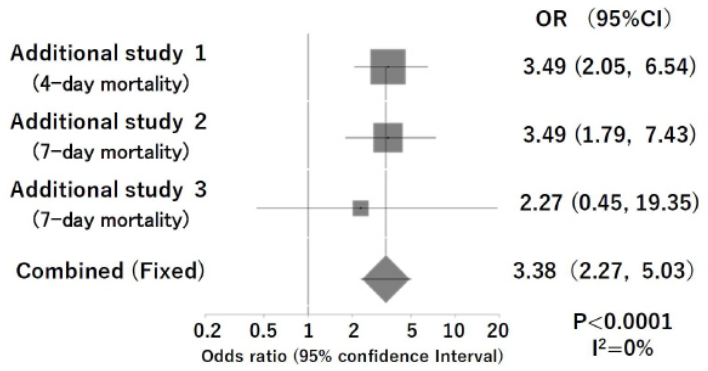
1.4. Increasing neonatal mortality trend observed even at the lowest dose of 0.1mg/kg/day

Additional Experiment 3 (STED p165) was conducted to obtain approval in Japan. In this study, inactive ingredients (control group), paroxetine 0.1 mg/kg, 1 mg/kg, and 13 mg/kg were orally administered to female rats from day 6 of gestation to day 20 postpartum. The 13 mg/kg group received a reduced dose of 1 mg/kg/day from day 19 of gestation to day 6 postpartum. The experiments investigated the effects on pregnant and lactating females, as well as on the occurrence and survival of embryos and offspring in the first (F1) generations. Analysis of data for the second (F2) generation was omitted because no method was provided.

For the F1 generation, the 7-day mortality rates calculated using the same method as in the main experiment were 0.8%, 1.3%, 1.8 and 3.1%, respectively. Trend analysis using the Chi-square test for linear trend showed a significant dose-dependent increase in the 7-day mortality rate (p=0.0189), with a significant increase observed in the 13 mg/kg group (odds ratio = 3.97, 95%CI: 1.05-14.95,p=0.028).

Howevr, STED stated that 1.0 mg/kg was the non-toxic dose for the newborns and the New Drug Application Review Report [4] do not mention the misinterpretation of the data.

Figure 2: Meta-analysis of neonatal 4-day or 7-day mortality of infants born from mothers exposed with paroxetine 1 mg/kg during pregnancy



Created by using the data in Table D-15 on p155-156, Table D-20 on p164 and Table D-21 on p166 of STED for Paxil. The method for estimating the number of births and 4-day deaths required to calculate the odds ratio is described in the footnotes (calculation of "4 day mortality (M) ") of the Supplementary tables on page 43-44.

1.5. Dose-dependent increase in infertility rate

Mating failure rates, calculated based on the initial number of rats in each group, were 6.7%, 16.7%, 33.3%, and 33.3% for the control, 4.3 mg/kg, 12.8 mg/kg, and 42.5 mg/kg groups, respectively (trend analysis: $p = 0.00475$). Infertility rates were 6.7%, 20.0%, 43.3%, and 56.7% for the same groups respectively (trend analysis: $p = 0.00001$). Both demonstrate significant dose-dependent increases.

The infertility rate relative to the number of matings also showed a significant dose-dependent increase. In the main experiment, the number of matings was 30, 29, 25, and 22, while the number of pregnant rats was 28, 24, 17, and 13 in the control, 4.3 mg/kg, 12.8 mg/kg, and 42.5 mg/kg groups, respectively. The number of infertile rats was 2, 5, 8, and 9 (trend analysis: $p = 0.00147$).

In rats, total resorption refers to the miscarriage of all fetuses. There were 0, 1, 2, and 2 cases of total resorption across the four groups. Trend analyses for total resorption (all miscarriages) relative to the number of pregnancies ($p = 0.0296$) and for the combined rate of infertility and total resorption (total miscarriage) relative to the number of matings ($p = 0.00014$) indicated statistically significant results.

1.6. Dose-dependent increase in post-implantation fetal loss

Although only the 35.3% rate in the high-dose group was reported as statistically significant in the STED (p154) [2], the data suggest a dose-response relationship, with post-implantation fetal loss rates of 7.3%, 13.0%, 30.7%, and 35.3% in the control, 4.3 mg/kg, 12.8 mg/kg, and 42.5 mg/kg groups, respectively. (The original data for acurate statistical analysis is unavailable.)

The STED (p154)[2] concludes that the no-observed-adverse-effect level (NOAEL) for general toxicity in parent animals is 4.3 mg/kg for males and below 4.3 mg/kg for females, while the NOAEL for fertility is 4.3 mg/kg for both males and females.

1.7. Low fetal weight is dose-dependent on paroxetine consumption

The mean fetal weight (range) in the control, 4.3 mg/kg, 12.8 mg/kg, and 42.5 mg/kg groups was 2.1 g (1.9–2.4), 2.0 g↓ (1.7–2.2), 1.9 g↓ (1.6–2.1), and 1.7 g↓ (1.0–1.9) respectively. These results demonstrate a significant and clearly dose-dependent decrease in fetal weight across the paroxetine groups (STED p154).

1.8. Increased infertility due to male paroxetine use

Additional Experiment 1 also aimed to determine whether infertility was caused by paroxetine use in males or females.

In the group where only males were administered 50 mg/kg of paroxetine, the copulating rate was 90% (18/20) compared with 100% (29/29) in the control group, showing a decreasing trend. The conception (pregnancy) rate in the male-only group was 75% (15/20) compared with 100% (29/29) in the control group, indicating an infertility rate of 25%. (Peto-OR = 14.48, 95% CI: 2.25–93.26, $p = 0.0049$). The infertility rate was higher (25%) when only males received 50 mg/kg compared with when only females were treated with 50 mg/kg, which showed an infertility rate of 12.5% (2/16).

1.9. Infertility persists even after 10 weeks of stopping paroxetine in males

In Additional Experiment 4 (STED p158), the conception rate in the group where only males were treated with 50 mg/kg of paroxetine dropped further to 53.3% (16/30), compared with 100% (30/30) in the control group. The conception rate remained at 50.0 % (15/30) at both week 3 and week 10 after discontinuing paroxetine. This indicates that when paroxetine is administered solely to males, about half of them experience infertility, which does not recover even after cessation of the drug. In this experiment, females unable to copulate were subsequently paired with other males for up to two weeks. This adjustment does not fully capture the male-induced non-copulation and infertility, so the actual copulation and conception rates would likely have been even lower without this intervention.

1.10. Decreased sperm count and reduced motility

In Additional Experiment 4 (STED p158), various parameters related to male reproductive health were also evaluated, including testis weight, sperm count, sperm motility, and pathology of the testes,

epididymis, and seminiferous tubules. The findings revealed a significant reduction in testis weight in the paroxetine group (3.04 g) compared with the control group (3.85 g). This reduction was accompanied by decreased sperm count and motility. Additional observations included swelling of the cauda epididymis, spermatocele formation in the epididymis, seminiferous tubule atrophy, and testicular degeneration. These changes did not resolve after treatment cessation but instead progressed. These findings suggest that the effects observed extend beyond reduced copulation ability or sexual drive, indicating that paroxetine induces significant organic damage or impairment of male reproductive function.

1.11. Skeletal abnormalities/variations observed

In the organogenesis phase study on SD rats (STED p161–162), distilled water was administered to the control group (17 rats), and paroxetine was administered to the treatment groups (20 rats in the 4.3 mg/kg group, 19 rats in the 12.8 mg/kg group, and 29 rats in the 42.5 mg/kg group) between gestational days 6 and 15. Although the STED stated that "no malformations due to administration of this drug were observed," one case of exencephaly was detected in the 12.8 mg/kg group after dissecting 146 rats. Furthermore, regarding "visceral malformations," only a total of 210 rats were examined (45 in the control group, and 46, 49, and 70 in the paroxetine treatment groups, respectively).

In general, ventricular septal defects occur in approximately 1 in 1,000 untreated rats [5]. To detect the toxicity of a drug that doubles the frequency (i.e., a 100% increase) using the same number of animals in both the control and drug groups, with $\alpha = 0.05$ and a power of 0.8, approximately 25,000 animals per group (a total of about 50,000 animals) are required (according to StatsDirect). To detect the toxicity of a drug that increases the defect occurrence tenfold, 1,272 rats per group (a total of 2,544 rats) are needed. Thus, a total of 210 rats is hardly sufficient for detection.

On the other hand, skeletal abnormalities, such as delayed ossification of the occipital bone and sternum, and shortened or small 13th ribs, were significantly increased in a dose-dependent manner. The number of abnormalities observed (and the frequencies per dam) were as follows: 8/114 (6.9%) in the control group, 12/114 (15.3%) in the 4.3 mg/kg paroxetine group, 21/96 (20.1%) in the 12.8 mg/kg group, and 24/131 (18.3%) in the 42.5 mg/kg group (trend analysis: $p = 0.00238$). Therefore, rather than ruling out the possibility of the major malformations, it is highly likely that they may occur.

2. Neonatal toxicity in humans

2.1. Withdrawal symptoms are a well-known phenomenon

It is widely recognized that withdrawal symptoms can occur when serotonin reuptake inhibitors (SRIs), including paroxetine, are discontinued [6-8]. Additionally, it is well established that benzodiazepine use during pregnancy can lead to withdrawal symptoms in the newborns [9]. As early as 1989, animal studies reported increased mortality in newborns within four days following intrauterine exposure to paroxetine [3]. These findings led to the conclusion that withdrawal symptoms were a contributing factor in these deaths.

2.2. Case reports have been documented since 1993

In 1993, a case report suggested that withdrawal symptoms in newborns could result from maternal use of fluoxetine hydrochloride (Prozac) during pregnancy [10]. In 1995, a case of suspected congenital sertraline dependence was reported [11]. In 1996, a review on the effects of serotonin reuptake inhibitors (SRIs) during pregnancy and breastfeeding highlighted instances of neonatal withdrawal symptoms [12].

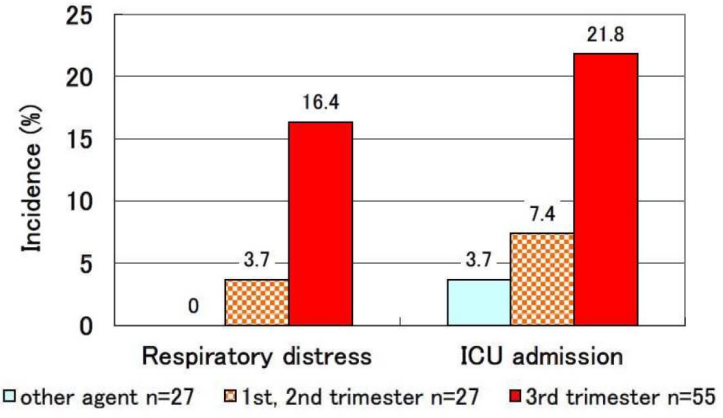
Another review on SRI withdrawal documented three cases of withdrawal symptoms in newborns [7].

According to PubMed, the first documented case of neonatal withdrawal symptoms specifically associated with paroxetine was published in 1997 [13]

2.3. Withdrawal syndrome observed in 22-23% of participants in a cohort study

In a 1996 cohort study [14] investigating fluoxetine use during pregnancy with a control group included, 23 out of 73 newborns (31.5%) whose mothers took fluoxetine during the third trimester exhibited poor neonatal adaptation. In contrast, none of the 220 newborns born to women in the control group who consumed only acetaminophen or small amounts

Figure 3: Paroxetine use during pregnancy and neonatal withdrawal toxicity (respiratory distress)



Created by using the data in Table 2 of Ref.15. Other agent: non-teratogenic agent (eg, acetaminophen or dental x-rays). 1st and 2nd trimester mean 1-week to 6-months gestational age.

of alcohol during pregnancy, experienced neonatal complications. Among newborns whose mothers took fluoxetine during the first or second trimester, 9 out of 98 (8.9%) showed poor neonatal adaptation.

The relative risk (RR) of neonatal complications for fluoxetine use during the third trimester compared with its use during the first trimester was 5.7 (95% CI: 2.5–13.1) based on univariate analysis and 8.7 (95% CI: 2.9–26.6) after adjustment using logistic regression. Furthermore, an analysis of the data provided in this report—an original analysis by the author that was not mentioned in the referenced paper—revealed that, compared with the control group, the relative risk for fluoxetine use during the third trimester was 144.2 (18.8–∞, $p < 0.0001$), and for use during the first or second trimester it was 42.3 (5.31–∞, $p < 0.0001$).

In 2002, another cohort study examined the outcomes of paroxetine use during pregnancy compared with a control group [15]. **Figure 3** shows the rates of respiratory distress (withdrawal symptoms) and ICU admission. The paroxetine group included 55 pregnant women who continued paroxetine use into the third trimester, while the control group consisted of 54 pregnant women—27 of whom had discontinued paroxetine during the first or second trimester and 27 who were taking medications which were considered as non-teratogenic. The groups were matched for age, number of pregnancies, number of deliveries, and alcohol or drug use.

Among the paroxetine group, 12 of 55 newborns (22%) required intensive care and long-term hospitalization. The most common condition was newborn respiratory distress syndrome, observed in 9 cases (16.4%); in one of these cases, the baby also presented with hypoglycemia. Additionally, there was one individual case each of bradycardia, hypoglycemia, and a feeding and swallowing disorder. In the control group, 3 of 54 newborns (5.6%) experienced complications (p=0.03). Among women who discontinued paroxetine during the second trimester, there was one case of newborn respiratory distress syndrome and one case of meconium aspiration syndrome. Among women taking non-teratogenic drugs, there were no cases of newborn respiratory distress syndrome and one case of jaundice. Preterm birth occurred significantly more often in the paroxetine group (20%) than in the control group (3.7%, p=0.02).

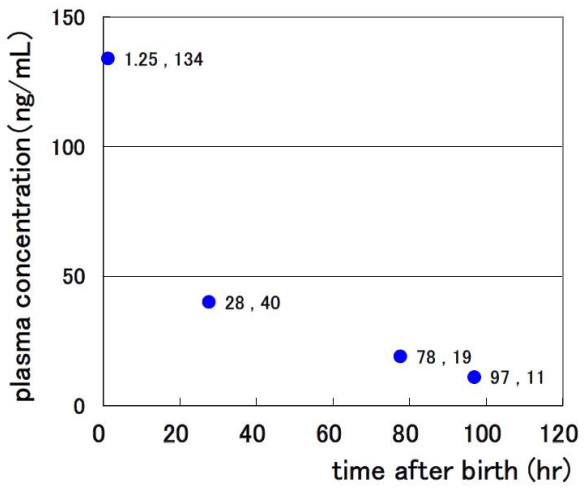
Analysis of risk factors for newborn respiratory distress syndrome identified paroxetine use during the third trimester as a significant factor. The crude odds ratio was 10.35 (1.27–84.67), and the adjusted odds ratio was 9.53 (CI: 1.14–79.3).

2.4. Approximately 70% of WHO SRI monitoring reports are for Paroxetine

An analysis of the database from the WHO Adverse Reaction Monitoring Center [15] identified 93 neonatal cases of suspected SRI withdrawal syndrome with assessable causal relationships reported since the system started until November 2003. Of these cases: 64 (69%) were related to paroxetine; 14 to fluoxetine; 9 to sertraline; and 7 to citalopram; including 1 case involving a combination of paroxetine and fluoxetine. Among these cases, 74 were classified as “certain”, 10 as “doubtful”, and 10 as “probably not”. Of the 74 certain cases, paroxetine was the most common, accounting for 51 cases (69%).

Reported number of adverse reactions included 158 Neurological symptoms (65 withdrawal syndrome, 27 nervousness, 11 convulsions, 11 hypertonia, 6 tremor, 5 involuntary muscle contractions, and 4 agitation etc) and 9 Respiratory symptoms (2 respiratory depression, 1

Figure 4: Plasma concentration (ng/mL) of paroxetine in a neonate



Created by using the data in Table 1 of Ref.22.

each for failure to thrive, apnea, dyspnea, hypoventilation, cyanosis etc). Other symptoms include 6 hypothermia, 1 each for encephalopathy, circulatory collapse, coma, and atrial septal defect etc.

Paroxetine held a relatively small share of the global SRI and SNRI market, representing only 21.7% of the total $265.2 billion market in 2001 and 2002 (as estimated by the author using data from [17]). Assuming that all SRI/SNRI drugs are priced equivalently, the odds ratio was estimated to be 8.0 (4.8–13.7).

2.5. Neonatal plasma paroxetine levels following maternal use are extremely high

Several case series have reported neonatal outcomes following maternal SRI use [18-21].

Additionally, one documented case measured neonatal plasma drug levels and correlated them with the progression of symptoms [22]. In this case, a pregnant woman received paroxetine at a dose of 15 mg per day starting at 28 weeks of gestation. The baby was delivered with Apgar scores of 9 at both 1 and 5 minutes. However, the doctor observed that the newborn exhibited symptoms including gasping for breath, pallor, hypotonia, arrhythmia, and acute respiratory distress. At 1.25 hours after birth, the paroxetine blood concentration was measured at 134 ng/mL. The infant was admitted to the ICU, and at 5 hours after birth, hypertonia increased and opisthotonos developed. Feeding became possible 52 hours after birth, and the baby was discharged 4 days later.

Figure 4 depicts the changes in paroxetine plasma concentration based on data from the article [22], which were originally reported in nmol/L and have been converted to ng/mL for clarity.

The neonatal plasma concentration of paroxetine immediately after birth was comparable to the steady-state concentration (130–240 ng/mL) observed in adults taking 40 mg daily for 10 days, and it gradually declined with an elimination half-life of 15–27 hours. Fetuses were exposed to high concentrations of paroxetine in utero, and as blood levels decreased after birth, these effects became pronounced. Notably, paroxetine is known to cause withdrawal symptoms in adults, which suggests that the observed effects are due to withdrawal. However, some aspects point to potential toxicity rather than mere withdrawal. Respiratory distress occurred approximately 1 hour after birth, and convulsions began at 5 hours post-birth while paroxetine plasma concentrations were still at 113 ng/mL. The infant regained the ability to feed only when the blood concentration dropped below 40 ng/mL. These observations suggest that poisoning, rather than withdrawal alone, may have been involved [22].

In this case, the infant was discharged after 5 days. However, another report described an infant exposed to 20 mg of fluoxetine daily during the second and third trimesters. That infant exhibited irritability, hypertonia, nervousness, and eating difficulties from the first day of life, with symptoms persisting for 6 weeks [23]. This underscores the need to consider that such symptoms may persist for an extended period.

2.6. The minimum lethal blood concentration of paroxetine is close to the therapeutic range

A forensic study reported on 168 fatal cases involving SRI use [24]. Among these, 60 cases involved fluoxetine, 5 involved fluvoxamine, 75 involved sertraline, and 28 involved paroxetine. In cases without other contributing risk factors, the lowest plasma concentrations associated with fatal outcomes were 630 ng/mL for fluoxetine, 400 ng/mL for paroxetine, and 1500 ng/mL for sertraline.

In the previous example referenced, the neonatal

blood concentration reached approximately one-third of the minimum lethal concentration for paroxetine, suggesting a potential risk of fatal poisoning due to in utero exposure.

2.7. 25 times greater risk of persistent pulmonary hypertension in newborns

A 1996 cohort study [14] reported persistent pulmonary hypertension of the newborn (PPHN) in 2 of 73 neonates (2.7%) whose mothers were administered paroxetine during pregnancy. This rate is significantly higher than the estimated prevalence of PPHN in the general population, which is 0.07–0.1% [14]. Building on this preliminary finding, a case-control study further investigated the association between SRI use and PPHN [25]. The study examined the medical histories of 377 mothers of neonates with PPHN (the PPHN group) and 836 matched mothers in a control group. Throughout the entire pregnancy, no significant difference was observed in the use of non-SRI antidepressants between the PPHN and control groups. However, SRI use tended to be more frequent in the PPHN group, although this difference was not statistically significant.

Some of the SRI-related results from [25] are shown in the Table. Fourteen neonates (3.7%) in the PPHN group were exposed to SRIs during the second half of pregnancy (after 20 weeks of gestation), compared with six neonates (0.7%) in the control group, resulting in an adjusted odds ratio of 6.1 (95% CI: 2.2–16.8). Sertraline had a Peto odds ratio (OR) of 8.98 (95% CI: 2.18–37.00, p = 0.0024), and paroxetine had a Peto OR of 25.2 (95% CI: 3.02–209.7, p = 0.0029), indicating a significant risk.

The article [25] did not explore the mechanisms underlying PPHN. However, hypoxemia resulting from sleep apnea syndrome is known to be associated with non-cardiogenic (reversible) pulmonary edema [26], which can lead to pulmonary hypertension. Similarly, persistent hypoxemia due to altitude sickness is widely recognized as a cause of compensatory pulmonary hypertension [27]. Furthermore, hypoxemia may stimulate serotonin-induced proliferation of pulmonary artery smooth muscle cells, contributing to pulmonary hypertension [28]. As a withdrawal symptom of SRIs, such as paroxetine, hypoxemia caused by respiratory distress may prolong respiratory issues, potentially leading to pulmonary hypertension through these mechanisms.

Additionally, SRIs such as paroxetine inhibit the uptake of serotonin in platelets [29], reducing ADP activation, which is necessary for hemostasis, thereby decreasing platelet aggregation and increasing bleeding tendencies [29]. A rapid decrease in SRI plasma levels during withdrawal could reverse this effect, enhancing coagulation and leading to the formation of microthrombi in the pulmonary arteries, thereby increasing pulmonary arterial pressure.

Furthermore, paroxetine is metabolized solely by the enzyme CYP2D6, and significant individual variability in response is common.

As pulmonary hypertension progresses, it may hinder the natural closure of the foramen ovale and ventricular septal defects, thereby increasing the

Table: Use of SRIs during Pregnancy by Mothers of Infants with PPHN and Matched Controls.

Maternal use of SRIs	Definite PPHN (N=377)	Matched Control (N=836)	Odds ratio (95%CI)	
			Crude OR	Adjusted OR
	no. (%)	no. (%)		
Never during pregnancy	361(95.8)	812(97.1)	1	1
Before wk 20	2 (0.5)	18 (2.2)	0.3 (0.1–1.1)	0.3 (0.1–1,2)
After wk 20	14 (3.7)	6 (0.7)	5.1 (1.9–13.3)	6.1 (2.2–16.8)
Fluoxetine	3 (0.8)	4 (0.5)	1.74 (0.35–8.65) *a	
Sertraline	**7 (1.9)**	**2 (0.2)**	**8.98 (2.18–37.00) *a**	
Paroxetine	**4 (1.1)**	**0**	**25.17 (3.02–209.7) *a**	

*a : Data without *a are from the Table 2 of ref. 25). Crude odds ratio with *a are the Peto odds ratios and 95% confidence intervals for individual drugs calculated using the data from Table 2 in the ref. 25).

risk of permanent abnormalities such as atrial or ventricular septal defects.

It is important to consider that relatively mild abnormalities caused by early pregnancy exposure to SRIs, particularly paroxetine, may be exacerbated by the effects of withdrawal.

2.8. Concerns about impact on neuropsychiatric development

Children chronically exposed to SRIs in utero, and thus dependent on them, who experience severe adverse withdrawal reactions—such as convulsions, apnea, encephalopathy, circulatory collapse, and coma—may face disruptions in the normal development of their serotonin system. There is concern that such disruptions could lead to injuries or impairments in mental and neurological development. When citalopram was administered during the neonatal period (8 to 21 days after birth), rats later exhibited increased locomotor activity and reduced sexual behavior [31]. This suggests that early-life exposure to SRIs may disrupt the normal development of the serotonin system, resulting in alterations to serotonin-dependent neuronal processes.

3. The information in the Japanese package insert is incomplete

Regarding pregnancy, the Japanese package insert for paroxetine issued in 2009 states the following:

9.5 Pregnant women

For pregnant women or women who may become pregnant, this drug should be administered only if it is determined that the therapeutic benefits outweigh the risks. If pregnancy is discovered during treatment, administration should be discontinued, or an alternative treatment should be implemented unless continued administration is deemed therapeutically appropriate.

9.5.1 Overseas epidemiological studies have shown an increased risk of congenital abnormalities, particularly cardiovascular abnormalities (e.g., ventricular or atrial septal defects), in newborns born to women who received this drug during the first trimester of pregnancy. One study reported that the incidence of cardiovascular abnormalities in newborns is approximately 2% when exposed to paroxetine compared with approximately 1% in the general population.

9.5.2 Respiratory depression, apnea, cyanosis, tachypnea, epileptiform seizures, tremor, muscle hypotonia or hypertonia, hyperreflexia, twitching, irritability, persistent crying, lethargy, somnolence, fever, hypothermia, feeding difficulties, vomiting, and hypoglycemia have been reported in newborns delivered by women who received this drug late in pregnancy. Many of these symptoms occur immediately or within 24 hours after delivery. However, some reports attribute these symptoms to neonatal asphyxia or drug withdrawal symptoms.

9.5.3 An overseas epidemiological study also indicated an increased risk of persistent pulmonary hypertension in newborns born to women who received selective serotonin reuptake inhibitors (including this drug: paroxetine) after the 20th week of pregnancy.[1),2)]

The Japanese package insert for paroxetine issued in 2025 adds the following sentences at the end of section **9.5.3.**

One of these studies, the risk ratio for persistent pulmonary hypertension in newbornes born after 34 weeks of gestation was 2.4 (95% CI: 1.2-4.3) when administered in early pregnancy and 3.6 (95% CI: 1.2-8.3) when administered in both early and late pregnancy.[2)]

References for the package insert of paroxetine.

1) Chambers CD, et al. N Engl J Med. 2006;354:579-587.
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These newly added descriptions are extremely misleading. The first half of section 9.5.3 of the package insert states that administration of SRI after week 20 of gestation increases the risk of PPHN. On the other hand, the second half only presents the risk ratios for administration during early pregnancy and for both early and late pregnancy combined. The adjusted risk ratio for administration during late pregnancy (after week 20) is 6.1 (95% CI: 2.2-16.8), and 25.17 (95% CI: 3.02-209.7) when specifically paroxetine was adninistered (see Table, p40) based on the ref. 25), which is the same source as the ref. 1) cited in the package insert.

Moreover, above descriptions are not included in the sections for Warnings, Contraindications, Precautions

for Use, Important Precautions, or Serious Side Effects. Instead, they are relegated to the latter half of the package insert under “Administration to Pregnant, Parturient, and Breastfeeding Women.”

Paroxetine should be contraindicated not only during pregnancy but also for women capable of becoming pregnant. If the drug is currently being used, the dosage should be gradually reduced and eventually discontinued. Additionally, the insert should clearly state: The increased risk of congenital abnormalities; The high incidence of severe neonatal withdrawal symptoms, reported at 22–32%; A 25-fold increase in the risk of persistent pulmonary hypertension in newborns.

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Table S1: D-14 Fertility and other general fertility test (1) on p153-154 of STED

Table D-14 Fertility and other general fertility test (1) on p153-154 of STED

animals used			SD rats. Male:110–155g, females:160–200g (at comncement)			
methods and duration of administration			forced oral administration of 10mL/kg once a day, males: 10 weeks before pairing for females to end of pairing period. females: 2 weeks before pairing for males to pregnant day 18 (cesarian section group) or to 23 days after delivery (spontaneous delivery group).			
Dose (mg/kg/day)			0 (distilled water)	4.3	12.8	42.5
male animals	number of rats		30	30	30	30
	number of death (cause of death)		0	1 (adm. error)	4 (adm. error)	8 (adm. error)
	body weight (day1 to day70		133.7→331.5	135.7→337.6	132.5→314.6 ↓	132.3→270.9 ↓
	mating rate (%)		93.3	86.2	80.0	90.9
	pregnancy rate (%)		93.3	82.8	68.0 ↓	59.1 ↓

Pregnancy day 0: day of mating, Cesarean section: day 19 of pregnancy, weaning date: day 23 after delivery. Average value.
Conception rate: (number of pregnancies / number of matings) x 100

Dose (mg/kg/day)			0 (distilled water)	4.3	12.8	42.5
female animals	number of rats		30	30	30	30
	number of death (cause of death)		0	0	1 (adm. error)	3 (adm. error)
	number of animals paired		30	29	25	22
	number of pregnant animal	cesarian section	14	12	9	8
		spontaneous delivery	14	12	8	5
	body weight	day1 to day14	177.8→192.7	178.5→197.5	179.0→191.0	180.4→182.6 ↓
		pregnant day 0 to 19	195.4→276.2	199.4→283.3	192.1→265.6	182.7→229.6 ↓
		after delivery 1 to 4	213.2→223.6	223.3→225.0 ↓	215.0→215.6 ↓	193.0→191.0 ↓
	gestation length (days)		21.7	21.6	21.3	21.4
	numberof corpus luteum #1 a)		13.4	14.1	14.3	13.0
	number implanted a)		10.8	11.3	9.7	7.4
	number of mother animals with total fetal absorption		0	1	2	2
fetus (F1)	number of alive fetus a)		10.0	10.6	8.4	5.9 ↓
	sex ratio (male/female)		5.6/4.4	4.8/5.8	4.4/4.0	3.1/2.8
	death rate before implantation (%) a)		20.6	13.1	15.3	37.7
	death rate after implantation (%) a)		7.3	13.0	30.7	35.3 ↑
	fetal body weight (g) a) (range of average BW in one mother)		2.1 (1.9–2.4)	2.0 ↓ (1.7–2.2)	1.9 ↓ (1.6–2.1)	1.7 ↓ (1.0–1.9)
	External system	malformation frequency(%) #2	0/140	2/127(1.2)	0/76	1/47(2.1)
		type		edema		omphalocele
		variation	–	–	–	–
	Internal organ	malformation frequency(%) #2	0/58	0/39	0/24	0/14
		variation				
	Bone system	malformation	none	none	none	none
		variation frequency(%) #2	4/82 (6.2)	13/86 (16.4)	7/52 (13.5)	4/32 (12.4)
		type	Unossified occipital bone, delayed ossification of thoracic vertebrae	Unossified occipital bone, delayed ossification of thoracic and lumbar vertebrae	Unossified occipital bone, delayed ossification of occipital and thoracic vertebrae	Unossified occipital bone, delayed ossification of thoracic vertebrae
Neonates (F1)	number of births		10.2	8.4	10.8	7.6
	sex ratio (male/female)		4.9/5.4	4.8/3.7	5.5/5.3	3.4/4.2
	birth rate (%) b)		100.0	77.6	96.9	69.4
	4-day survival rate (%) #3, b)		88.5	30.9 ↓	13.5 ↓	0.0 ↓
	weaning rate (%)		63.0	17.8 ↓	8.3 ↓	0.0 ↓
	body weight at weaning		38.3 (m,f)	33.8 (m,f)	45.9 (m,f)	no data #5
	physical development and differentiation #4		–	–	–	
non-toxic dose		parent animal	general toxicity: male:4.3mg/kg, female: less than 4.3mg/kg, fertility: 4.3mg/kg (male and			
		F1	fetus and neonates: less than 4.3mg/kg			

death rate before implantation=(number of corpus luteum–number implanted)/number of corpus luteum x100 (%)
death rate after implantation = (number implanted– number of alive fetus)/ number of implanted x100 (%)
#1: numbers were not determined in mother animals with total fetal absorption.
#2: number of animals with abnormality/examined (numbers of parenthesis are frequency in one mother animal
#3: calculated based on the births.
#4: opening of auricle, fur growing, budding of incisor and opening of eye (only one mother animal as for 15mg/kg)
#5: because all neonates died
–: no abnormal findings ↑: high (significantly) ↓: low (significantly),
a): Kruskal-Walis test and Jonckheer test (vs control) **b):** Williams test (vs control),
STED: Summary Technical Documentation (for Paxil),

Calculation of "4 day mortality (M)" added by Hama R.

		Control	4.3mg/kg/day	12.8 mg/kg/day	42.5 mg/kg/day
①	Number of pregnancies	28	24	17	13
②	Number of mothers with total embryonic deaths	0	1	2	2
③	Number of mothers with live births	28	23	15	11
④	Number of newborn	10.2	8.4	10.8	7.6
⑤	Number of estimated newborn = ③ × ④	285.6	193	162	83.60
⑥	4-day survival rate (%)	88.5	30.9	13.5	0.0
⑦	Estimated number survived at day 4 = ⑤ ×⑥/1	253	60	22	0
⑧	Estimated number of deaths during 4 days	32.8	134	140	83.60
M	4-day mortality rate = ⑧/⑤×100	**11.5**	**69.1**	**86.5**	**100.0**

"4-day mortality rate (M)" was calculated by the followings:
① pregnant mothers – ② Number of mothers with total embryonic deaths = ③ Number of mothers with live births, ④ number of newborn, ⑤ number of estimated newborn= ③x④, ⑥ 4-day survival rate (%), ⑦ number survived at day 4 = ⑤ ×⑥/100, ⑧ 4-day deaths = ⑤– ⑦, **(M)** 4-day mortality rate =⑧/⑤×100 (%).

Table S2: D-15 Fertility and other general fertility test (2) on p155-156 of STED

animals used		rats : Wister FU (RORO) strain. BW: Male:114–159g, females:116–148g (at allocation)		
methods and duration of administration		forced oral administration of 10mL/kg once a day, males 9 weeks berofe pairing to the end of pairing period (in the control and 50mg/kg group, treatment were continued and after 23 weeks, stopped for 3 weeks) . females: 2 weeks (7 weeks of study) before pairing to day 19 (cesarian section group) or to 23 days after delivery (spontaneous delivery group). (in the spontaneous delivery group, treatments were given for 24 weeks of study and were autopsied (cf: study day0=the day of comencement in the male group)		
male: dose (mg/kg/day)		0 (distilled water)	1	50
number of animals		30	30	20
male animals	number died or emergency slaughtered weeks found, findings of autopsy	0	1 5w, pulmonary edema	5 12–23w, pulmonary edema in 3 rats
	general conditions	–	–	irritability, salivation, dirty fur, dyspnea, seizure (8w–)
	body weight (d0 to w10)	188 → 365	184 → 364	185 → 287 ↓
	testis weight (n=10) **a)**	4.8	4.7	not done
	autopsy findings for alive cases (number of cases)	–	lobar consolidation(2) petechae(3)	not done

pregnant day 0: the day of mating. **#:** for control and 50 mg/kg group, 11 weeks after administration
–: no abnormal findings ↓: low (significantly), **a)**: student t–test (vs control)

female: dose (mg/kg/day)			0 (distilled water)		1	50	50
number of animals			30	20	30	20	20
dose level for paired male (mg/kg/day)			0	50	1	50	0
female animals	number of pregnant animal	cesarian section	20	20	20	20	20
		spontaneous delivery	10	0	10	0	0
	number died or emergency slaughtered		1		2	6	
	weeks found, findings of autopsy		16w: induration in mamary gland, adhesion of peritoneum		1:before treatment, 11w: consolidation, adhesion, dyscoloration in right lobe, aneurysm in hepatic artery	8–16w: pulmonary edema in 4 cases	
	general conditions		–		–	irritability, salivation, dirty fur, dyspnea, seizure	
	body weight (g)	before pregnancy	198 → 218		196 → 221	197 → 191 ↓	
		during pregnancy **#1**	218 →324	226→321	227→328	201→266 ↓	201→279 ↓
		after delivery **#2**	262→303	ND	259→307	ND	
	mating rate (%)		100	90.0	96.4	94.4	93.8
	pregnancy rate (%)		100	75.0	96.4	66.7	87.5
	gestation length (days)		21.5	ND	21.5	ND	ND
	numberof corpus luteum		14.3	13.0	14.6	7.8	13.5
	number implanted		11.9	9.7	12.6	3.9 ↓	9.9
	delivery rate (%)		100	ND	100	ND	ND
	autopsy findings for alive cases (number of cases) **#3**		–	–	–	–	–
F1 fetus	number of alive fetus **b)**		10.8	8.5	11.6	2.4	7.6
	sex ratio (male/female)		5.8/5.0	4.1/4.5	5.4/6.3	1.6/0.8	3.7/3.9
	death rate before implantation (%) **b)**		17.0	26.3	15.0	49.9 ↑	21.6
	death rate after implantation (%) **b)**		9.8	17.0	10.1	72.2 ↑	30.3
	fetal body weight (g) **b)** (range of average BW in one mother)		3.30	3.44	3.22	3.32	2.57 ↓
	external malformation (number of cases)		multiple finger (4)	–	–	–	Hindlimb malrotation (1)
F1 Neonates	number of births **c)**		10.8	ND	10.2	ND	
	rate of birth (%) **c)**		100		97.7		
	4–day survival rate (%) c)		93.9		81.5		
	21–day survival rate (%) **c)**		91.4		76.7		
	sex ratio (male/female at weaning)		5.6/4.2		3.7/5.2		
	body weight		–		–		
	autopsy findings		–		–		
non–toxic dose			for female parents' general toxicity and F1's toxicity: 1mg/kg,/day				

pregnant day 0 is the day mated. Cesarian section: on gestational day 20. Weaning day: postnatal day 21,
gestation rate: (number pregnant/number mated)x100
death rate before implantation=(number of corpus luteum –number implanted)/number of corpus luteum x100 (%)
death rate after implantation = (number implanted– number of alive fetus)/ number of implanted x100 (%)

#1: only of mother with Cesarian section and with live fetusss. **#2:** only mother rats with live newborn at weaning. **#3:** study week 25
–: no abnormal findings ↑: high (significantly) ↓: low (significantly) **a)**: Student t test (vs control) **b):** Kruskal–Walis test **c):** Wilkoxon test, **ND**: no data
STED: Summary Technical Documentation (for Paxi)I,

Calculation of "4 day mortality (M)" added by Hama R.

		control		1mg/kg/day	
①	Number of pregnancies	30		30	
②	Number of mothers with total embryonic deaths	0		0	
③	Number of mothers with live births	30		30	
④	Number of newborn	10.8		10.2	
⑤	Number of estimated newborn = ③ × ④	324		306	
⑥	4–day survival rate (%)	93.9		81.5	
⑦	Estimated number survived at day 4 = ⑤ ×⑥/10	304		249	
⑧	Estimated number of deaths during 4 days	20		57	
M	4–day mortality rate = ⑧/⑤×100	**6.1**		**18.5**	

"4–day mortality rate (M)" was calculated by the followings:
① pregnant mothers – ② Number of mothers with total embryonic deaths = ③ Number of mothers with live births, ④ number of newborn,
⑤ number of estimated newborn= ③x④, ⑥ 4–day survival rate (%), ⑦ number survived at day 4 = ⑤ ×⑥/100, ⑧ 4–day deaths = ⑤– ⑦,
(M) 4–day mortality rate =⑧/⑤× 100 (%) .

Memorial Tribute

Mr. Charles Medawar

A lifetime of activities breaking down barriers between patients and medical professionals

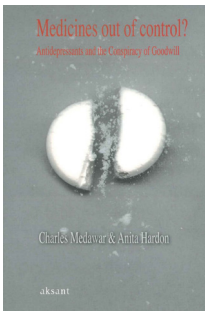
On 21 February 2025, Mr. Charles Medawar passed away at the age of 82.

He was the head of Social Audit, a non-profit private organization for consumer protection established in the UK in 1972. Among the many social issues, Mr. Medawar placed particular emphasis on the extent of damage caused by pharmaceuticals. From the mid-1980s onwards, he focused on pharmaceutical regulation and drug-related problems, working in cooperation with the International Society of Drug Bulletins (ISDB), of which this bulletin is a member.

In the 1990s, he offered sharp warnings about the medical and social issues surrounding the harm caused by benzodiazepines, which were widely used as so-called "tranquilizers" and "sleeping pills" among pharmaceuticals. He then turned his attention to the serious harm caused by SRIs (serotonin reuptake inhibitors), such as paroxetine (brand names "Paxil" or "Seroxat"), which were introduced later , and actively promoted awareness of the associated medical and social concerns. One of the key outcomes of this work was his great book, "Medicines Out of Control?".

"Japan is now moving toward the direction described in this book. What we have felt and raised concerns about in relation to the trends surrounding medicine in Japan is expressed here in easy-to-understand language, with highly persuasive analysis."

This was my first impression when I picked up the book. We invited him to contribute an editorial for the special feature on "Anxiety, Panic Disorders, and Medicines" in our bulletin "Check Your Medicines to Save Your Life" Issue No. 13 (published in January 2004) (reprinted on the next page). We also welcomed him as a guest speaker at the 4th Pharmacovigilance Seminar, "Can the Wall of "XYZ" Be Broken Down? Let's Reconsider EBM in Prevention and Treatment", held in November 2004. He gave a lecture titled "How to Remove the Barriers between Patients and Medical Professionals - Starting with the Approach to SSRIs".



Following the seminar, we started translating "Medicines Out of Control?" and were able to publish it in December 2005 by the NPO Japan Institute of Pharmacovigilance.

Mr. Medawar emphasized how important it is to collect reports from consumers in order to understand the harms caused by drugs, and highly valued our bulletin, which provides "scientific, unbiased drug information" to support this aim.

In keeping with his vision, we are committed to continuing to provide high-quality information in the future, and this is my tribute to Charles Medawar.
(Publisher, MedCheck HAMA, Rokuro)

The MedCheck editorial team sent our condolences to his family, and received the following reply, which we share here with their permission.

Dear Rohuro Hama,

Thank you so much for writing. I was very touched to receive your mail telling me how important Charles had been to your organisation and for the preface to the Japanese version of Medicines Out of Control. I do remember how important the visit to Japan was for him and how much he enjoyed your hospitality and your appreciation of his work. He often recalled the experience.

We organised a celebration of Charles's life and work and I received many letters from people from the many different organisations and trusts that he had set up or been associated with like Social Audit, Health Action International, and from individuals who valued Charles's contribution to their lives in so many different ways. He tended to make strong friendships and make an impact even with brief contacts with people. He was much loved and admired and will be very much missed.

With kind regards,

Caroline Medawar

Medicine consumers have a vital part to play

Charles Medawar
Director, Social Audit Ltd,
London UK

November 2003

As a firm believer in partnership between the providers and users of health system, I have long admired NPOJIP as an important source of independent drug information for both professionals and consumers. Professional expertise alone is not enough; medicine can only work within a democratic framework. The 19th century British philosopher, Samuel Butler, explained this well: "the public do not know enough to be experts, yet know enough to choose between them".

This issue of the journal deals with an especially timely and important issue-the effective use of drugs for anxiety, panic and related mental distress. Many people have benefited from the main drugs used to treat such complaints, the so-called SSRIs (selective serotonin reuptake inhibitors), but many others have experienced serious problems too. Sometimes intolerable withdrawal symptoms can make it hard and hazardous to stop taking these drugs and also expose many users to often severe and depressing side effects - substantial weight gain, loss of libido, mood changes and more. Suspicions about such problems - especially about drug-induced suicidal behaviour and sensitisation to depression - have existed for years, but searching investigations have only just begun.

When the truth about the benefits and risks of these drugs is finally revealed, I believe it will mark a turning point in the history of medicine. This is because of the recent and explosive growth of the Internet: it introduced quite new opportunities for gathering and exchanging evidence. It gave patients a collective voice that they never had before.

United by the Internet, many thousands of patients on SSRI drugs from all over the world began to describe experiences with these drugs and problems on withdrawal that were in advance of the scientific evidence, and which bore little resemblance to the official warnings. The impact of this user intelligence has been profound: in 2003, GlaxoSmithKline revised its 2002 estimate of the incidence of paroxetine withdrawal reactions from 0.2% to 25% (even as Pfizer continues to claim that its very similar drug product, sertraline, is "not habit forming" at all).

Now for the first time, we are seeing dramatic evidence of the collective value of user reports in understanding drug risk. This, in turn, underlines the great value of Kusuri-no-Check, in developing independent drug information for consumers, to help them contribute to the better development of medicine and health. I send congratulations and my very best wishes for the great success of all your future work.