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Pharmacological considerations in antipsychotic drug selection for prevention of drug-induced dysphagia

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Antipsychotic drugs have the ability to induce dysphagia. The aim of this study was to determine the association between the receptor affinity of antipsychotic drugs and the time-to-onset of dysphagia, and to identify factors that prevent antipsychotic drug-induced dysphagia. We used the receptor affinity of 13 antipsychotic drugs for which data were reported in an *in vitro* test using human receptors, extracted time-to-onset dysphagia from the Japan Adverse Drug Event Report database, and used data from 46 patients to evaluate the correlation between receptor affinity and time-to-onset of dysphagia. We found a negative correlation between D_2 receptor affinity and time-to-onset of dysphagia (r = –0.4572, p = 0.0016), and a positive correlation between H_1, M_1, and M_3 receptor affinity and time-to-onset of dysphagia (r = 0.5006, p = 0.0006; r = 0.4130, p = 0.0059; and r = 0.4149, p = 0.0057, respectively). Antipsychotic drugs with a strong D_2 receptor-blocking action may accelerate the onset of dysphagia, whereas a strong H_1, M_1, and M_3 receptor-blocking action may delay the onset of dysphagia. The current study revealed the relationship between the receptor affinity of antipsychotic drugs and the time-to-onset of dysphagia, which should aid in the selection of antipsychotic drugs, while preventing dysphagia.

1. Introduction

Dysphagia, or difficulty in swallowing, can lead to aspiration pneumonia, nutritional disorders, and difficulty with oral drug intake, which may have a significant negative impact on the quality of life of patients (Furuta and Yoshihisa 2013). The causes of dysphagia, which is a serious medical issue, especially in the elderly, can be divided broadly into two groups: structural lesions in the oral cavity, pharynx, esophagus, or other sites; and pathophysiological conditions, such as neuromuscular diseases (Aslam and Vaezi 2013). Importantly, among the pathological conditions, antipsychotic drugs have been reported to induce dysphagia in some patients (Sliwa and Lis 1993; Stewart 2003). Antipsychotic drugs are prescribed for the treatment of psychotic symptoms and agitation in patients with schizophrenia and dementia disorders, and are common in the medical care of the elderly (Carton et al. 2015). However, most studies on dysphagia due to antipsychotic drugs are case reports, and the selection of antipsychotic drugs with minimal or no drug-induced dysphagia has not yet been elucidated.

Although dopamine receptors are the only target receptors on which antipsychotic drugs exert their effects, the blockade of various other receptors is also related to swallowing. Blockade of the dopamine D_2 receptor suppresses swallowing *via* the extrapyramidal tract (O'Neill and Remington 2003). Blocking the H_1 and α_1 receptors has a sedative effect (Tokuda 2006), which consequently decreases concentration and appetite, and alters eating behavior (Linette and Peter 2007). Conversely, blocking 5-hydroxytryptamine 2A ($5HT_{2A}$) receptors by antipsychotic drugs reduces extrapyramidal symptoms *via* the D_2 receptor block (Tokuda 2006). Furthermore, blocking muscarinic receptors hinders bolus formation, due to the drying of the mouth, and suppresses swallowing via interference with esophageal muscles (Linette and Peter 2007), while reducing extrapyramidal symptoms, depending on the balance with dopamine in the central nervous system (Tokuda 2006). Antipsychotic drugs act on various receptors, although the strength of the action on each receptor is different for each antipsychotic drug. Therefore, antipsychotic drugs can be classified based on their affinity for each receptor. As the extent of the effect of an antipsychotic drug on the receptor is dependent on the receptor's affinity to the drug, the impact of the antipsychotic drugs on swallowing can be evaluated by the strength of this affinity.

A systematic review of oropharyngeal dysphagia induced by antipsychotic medications showed that the prevalence of dysphagia ranged from 21.9 to 69.5% (Miarons and Rofes 2017). Although the prevalence of adverse drug reactions may help to prioritize reactions that require monitoring, the prevalence of dysphagia is wide to be not helpful in monitoring dysphagia. In contrast, in clinical practice, it is important to know the time of the onset of the side effect (hereafter referred to as time-to-onset) to explain the causal relationship between antipsychotic drugs and side effects (Edwards and Aronson 2000). In the present study, time-to-onset was used as the endpoint. Antipsychotic drugs with a strong negative effect on swallowing are predicted to be associated with an earlier time-to-onset of dysphagia; conversely, antipsychotic drugs with a strong positive effect on swallowing are expected to be associated with delayed time-to-onset of dysphagia.

This study was conducted to examine the association between the receptor affinity of antipsychotic drugs and the time-to-onset of dysphagia based on data extracted from the Japan Adverse Drug Event Report database (JADER), with the aim of identifying factors that prevent antipsychotic drug-induced dysphagia.

2. Investigations and results

The K_i values of antipsychotic drugs for each receptor used in this study are shown in Table 1. Phenothiazine had high D_2 receptor affinity, but low M_3 receptor affinity. Serotonin-dopamine antagonists had high D_2 and $5HT_{2A}$ receptor affinity, and multi-acting receptor-targeted antipsychotics, except asenapine, had higher M_1 receptor affinity than D_2 receptor affinity.

Table 1: Receptor affinity of the antipsychotic agents included in the study

		Ki (nM)					
		D_2	H_1	α_1	$5HT_{2A}$	M_1	M_3
Phenothiazine	Chlorpromazine‡	1.5	7.0	0.6	7.9	ND	47.0
	Fluphenazine‡	0.2	24.4	13.6	29.7	ND	1441.0
	Perphenazine‡	0.5	9.3	20.9	5.5	ND	1848.0
Butyrophenone	Haloperidol	1.5	2090.0	25.1	52.5	5620.0	10000.0
Benzamide	Sulpiride§	21.5	ND	ND	ND	ND	ND
	Tiapride§	565.0	ND	ND	ND	ND	ND
SDA	Risperidone	6.2	81.3	5.1	0.2	10000.0	10000.0
	Paliperidone¶	1.1	23.4	5.2	0.7	5620.0	10000.0
MARTA	Clozapine	135.0	1.7	12.6	4.1	5.1	24.5
	Olanzapine	21.4	3.4	22.4	1.3	12.0	33.9
	Quetiapine	417.0	11.0	64.6	155.0	282.0	513.0
	Asenapine	1.3	1.0	1.2	0.1	8130.0	10000.0
DSS	Aripiprazole	1.2	20.4	324.0	9.6	3890.0	7760.0

All data without notes are based on Asenapine maleate (SYCREST®) Interview form, ‡ based on Kroeze et al. (2003), § based on Burstein et al. (2005), based on Gray et al. (2007)

The arrangement of antipsychotic drugs by principal component analysis, performed to classify antipsychotic drugs based on K_i values, is shown in Fig. 1. As the contribution ratios of components 1 and 2 were 45.8% and 29.9%, respectively, and the cumulative contribution ratio was 75.7%, we determined that components 1 and 2 were the main components. The D_2 receptor was placed on the minus side, and the H_1, M_1, and M_3 receptors were placed on the positive side of the horizontal axis (component 1). The $5HT_{2A}$, H_1, and α1 receptors were placed on the plus side of the vertical axis (component 2). Drugs placed on the negative side on the horizontal axis were asenapine, paliperidone, risperidone, perphenazine, fluphenazine, aripiprazole, and haloperidol. Drugs placed on the positive side of the horizontal axis were chlorpromazine, olanzapine, clozapine, and quetiapine. Sulpiride and tiapride were not placed on the figure because the data were obtained only for the D_2 receptor.

In total, 46 patients (28 men and 18 women) were included in the final analyses to evaluate the correlation between K_i and time-to-onset of dysphagia. The median age of the patients was 60 years (interquartile range, 30 years). The primary diseases in n ≥ 3 patients were bipolar disorder, cerebral infarction, dementia, depression, diabetes, hypertension, insomnia, parkinsonism, and schizophrenia. The antipsychotic drugs prescribed in this study included aripiprazole, clozapine, haloperidol, olanzapine, risperidone, sulpiride, and tiapride (Table 2).

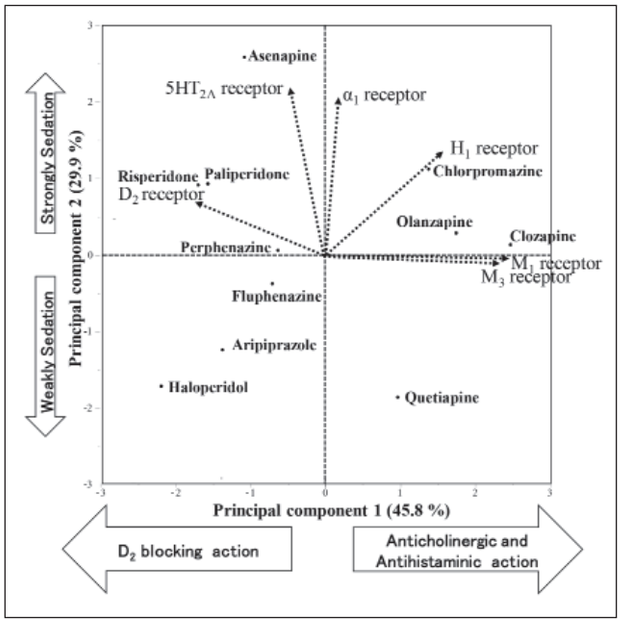

Fig. 1: Arrangement of antipsychotic drugs by principal component analysis based on receptor affinity

Table 2: Patient characteristics

Patients taking a single antipsychotic agent and developed drug-induced dysphagia	46
Male /Female	28 /18
Median age (IQR)	60 (30)
Typical /Atypical antipsychotic agent	9 /37
Primary diseases (n≥3)	Bipolar disorder, Cerebral infarction, Dementia, Depression, Diabetes, Hypertension, Insomnia, Parkinsonism, Schizophrenia
Antipsychotic drug	aripiprazole, clozapine, haloperidol, olanzapine, risperidone, sulpiride, tiapride

IQR: Interquartile range

The correlation between K_i and time-to-onset of dysphagia for each antipsychotic drug is shown in Table 3. We found a negative correlation between D_2 receptor affinity and time-to-onset of dysphagia ($r = -0.4572$, $p = 0.0016$). Conversely, we found a positive correlation between the H_1, M_1, and M_3 receptor affinity and time-to-onset of dysphagia ($r = 0.5006$, $p = 0.0006$; $r = 0.4130$, $p = 0.0059$; and $r = 0.4149$, $p = 0.0057$, respectively). There was no correlation between $5HT_{2A}$ or α_1 receptor affinity and time-to-onset of dysphagia.

Table 3: Correlation between the receptor affinity of each antipsychotic drug and the time-to-onset of dysphagia

	Correlation coefficient	
Receptor	r	p
D_2	- 0.4572	0.0016
$5HT_{2A}$	0.1159	0.4592
α_1	0.0661	0.6737
H_1	0.5006	0.0006
M_1	0.4130	0.0059
M_3	0.4149	0.0057

3. Discussion

In the current study, we investigated the relationship between the receptor affinity of antipsychotic drugs and the time-to-onset of dysphagia. The arrangement in principal component analysis showed that the interaction of the D_2 receptor was in the opposite direction to those observed with the H_1, M_1, and M_3 receptors, indicating that the blocking action of the D_2 receptors became stronger toward the negative side, whereas those of the H_1, M_1, and M_3 receptors became stronger toward the positive side of the horizontal axis. In addition, as H_1 and α_1 receptors were placed on the positive side on the vertical axis, the positive side indicated a strong sedative effect, whereas the negative side reflected a weak sedative effect.

There was a negative correlation between the affinity of antipsychotic drugs for the D_2 receptor and time-to-onset of dysphagia, and a positive correlation was observed between their affinity for the H_1, M_1, and M_3 receptors and time-to-onset of dysphagia. These results indicated that a stronger D_2 receptor blocking ability was associated with a shorter time-to-onset of dysphagia, and a stronger blocking ability of the H_1, M_1, and M_3 receptors was associated with a longer time-to-onset of dysphagia. Together with the results of the principal component analysis, these findings suggested that antipsychotic drugs with a strong D_2 receptor blocking action (asenapine, paliperidone, risperidone, aripiprazole, and haloper-

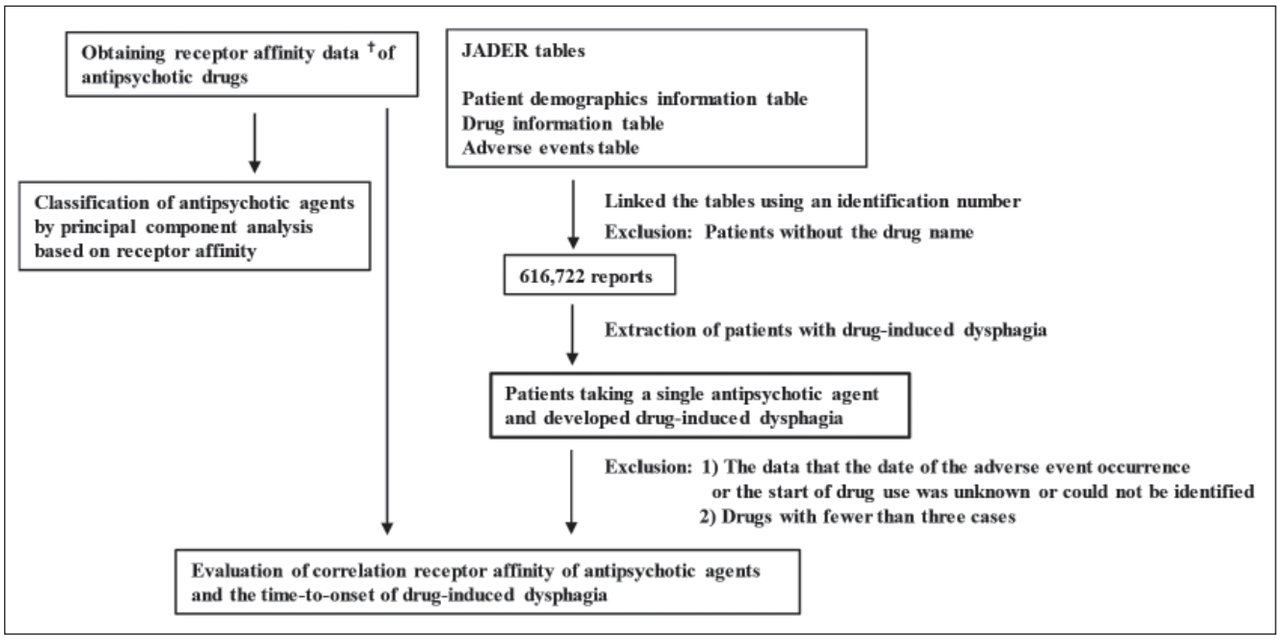

Fig. 2: The flow of analysis method of this research
†: D2, H1, a1, 5HT2A, M1, M3 receptor

idol) may accelerate the onset of dysphagia, whereas antipsychotic drugs with strong H_1, M_1, or M_3 receptor blocking action (chlorpromazine, olanzapine, clozapine, and quetiapine) may delay the onset of dysphagia. From a pharmacological perspective, blocking the H_1 receptors adversely affects swallowing caused by a sedative effect. Blocking the M_1 and M_3 receptors has negative effects on swallowing by preventing bolus formation due to dry mouth and suppressing swallowing by interference with the esophagus muscle in the peripheral nervous system, as well as positive effects on swallowing by reducing extrapyramidal symptoms in the central nervous system. However, our results indicated that blocking the M_1 and M_3 receptors had a positive effect on swallowing. Therefore, at least regarding the ability of antipsychotic drugs to block M_1 and M_3 receptors, a drug with a relatively strong central anticholinergic effects may be useful for the prevention of drug-induced dysphagia.

Studies that have reported on time-to-onset of dysphagia associated with antipsychotic drugs (O'Neill and Remington 2003; Dziewas et al. 2007; Nozaki and Katsuragi 2014), have not discussed the difference in time-to-onset of dysphagia by drug type. The current results revealed an association between receptor affinity and time-to-onset of dysphagia, and indicated that the differences in time-to-onset of dysphagia among antipsychotic drugs can be predicted based on receptor affinity. Thus, appropriate drug selection, based on these differences, may be possible to prevent drug-induced dysphagia.

Conversely, antipsychotic drugs have several other side effects, such as hypotension and arrhythmia in the circulatory system, and weight gain in the endocrine system. Therefore, the current results should be interpreted with consideration of these side effects before applying the findings to drug selection. For example, chlorpromazine appears to be an appropriate choice for the prevention of dysphagia, because it delays the time-to-onset of dysphagia; however, it has known side effects on the cardiovascular system. Therefore, one should be cognizant of this when chlorpromazine is considered the first choice in patients with cardiovascular disease.

The current study had several limitations. First, the method of linking receptor affinity to side effects was modeled according to the method of Kroze et al. (2003). However, this method is limited as it considers receptor affinity data as a drug property and does not take into account the half-life, receptor occupancy, and penetration through the blood-brain barrier, which alter the effect of antipsychotic drugs. Second, the primary diseases of the eligible patients (Table 2) were not biased toward diseases affecting dysphagia, such as cerebral infarction. Moreover, patient factors that influenced pharmacokinetics, such as hepatic and renal function, were not known. Therefore, future studies should consider the influence of these factors. Third, spontaneous reporting databases are generally associated with reporting bias, such as underreporting (Sakaeda et al. 2013; Bate and Evans 2009), data loss (Sakaeda et al. 2013), increased reporting rates for topical adverse events (notoriety and ripple effects) (Sakaeda et al. 2013), and duplication of reports (Bate and Evans 2009). Therefore, caution is warranted when interpreting the results obtained from the JADER. This was a small study (n=46) and several cases did not include full data, including descriptions related to the number of days, treatment start date, or date of onset for the adverse event. Therefore, future studies are necessary to verify the current findings using additional data, such as those derived from patient charts and other databases. Nevertheless, the current study indicated the relationship between drug characteristics derived from the receptor affinity of specific antipsychotic drugs and the time-to-onset of dysphagia, which should assist in the selection of antipsychotic drugs while minimizing the incidence of dysphagia.

4. Experimental

A flow chart of the analysis methods used in this research is presented in Fig. 2.

4.1. Collection of data on the receptor affinity of antipsychotic drugs

In the current study, we used the inhibition constant (K_i) of 13 antipsychotic drugs for which data were reported in an *in-vitro* study using human receptors based on the interview form (Meiji Seika Pharma 2018) and the literature (Kroeze et al. 2003; Burstein et al. 2005; Gray and Roth 2007). K_i indicated whether the test drug inhibited the binding between the labeled drug and the receptor: a smaller K_i value indicated a stronger drug affinity for the receptor. According to the method defined by Kroeze et al. (2003), a maximum K_i value of 10,000 nM was used for low-affinity interactions. These studies were performed independently to minimize the variability of measurement conditions. We converted the K_i value of each antipsychotic drug reported in these studies, based on the ratio of the K_i value of haloperidol and asenapine maleate (SYCREST®), according to the method of Sekine et al. (1999). In the current study, the receptors of interest were D_2, H_1, α_1, $5HT_{2A}$, and muscarinic receptors. Among the five muscarinic receptor types (M_1 to M_5), the M_1 receptor, which is highly prevalent in the striatum (Levey 1993), and the M_3 receptor responsible for salivary secretion (Matsui et al. 2000) were targeted in the current study. When no receptor affinity data were available, the K_i value was reported as missing.

4.2. Classification of antipsychotics drugs based on receptor affinity K_i values

We used principal component analysis to classify antipsychotic drugs based on K_i values. Principal component analysis is a multivariate analysis method that can

explain the whole by contracting multidimensional variables to low-dimensional variables. In the current study, we considered the number of principal components where the cumulative contribution ratio of principal components was ≥70%. We identified the characteristics of the antipsychotic drugs in the current study by classifying the 13 antipsychotic drug types based on the principal component score and six receptors based on the principal component loading.

4.3. Identification of time-to-onset of dysphagia

We used information from the JADER database between April 2004 and December 2019 to extract data on patients treated with antipsychotic drugs as single agents and to investigate the time-to-onset of dysphagia. JADER data, which is owned by the PMDA, can be accessed directly at http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp. We first combined data from cases with drug information and adverse events by excluding those cases without drug names in the drug information tables. Adverse event definitions in the JADER were based on the Preferred Term section of the Medical Dictionary for Regulatory Activities/Japanese version 20.0 (MedDRA/J Ver. 20.0). In the current study, the adverse events analyzed as drug-induced dysphagia included "foreign body aspiration," "aspiration," and "dysphagia." Time-to-onset was defined by subtracting the date of drug initiation from the date of the adverse event.

Next, from the combined data, we extracted records for patients on a single antipsychotic treatment with dysphagia. We excluded patients with missing or unknown adverse events and drug treatment start dates, and patients using sustained-release products. Furthermore, to ensure the reliability of the data, drugs that were administered in fewer than three patients were excluded.

4.4. Evaluation of the correlation between receptor affinity K_i values and time-to-onset of dysphagia with antipsychotic drug use

K_i was treated as the reciprocal value because the receptor affinity increased with a decrease in K_i. To evaluate the correlation between receptor affinity and time-to-onset of dysphagia, we used the Pearson correlation coefficient.

4.5. Statistical analysis

Statistical analysis was performed using JMP 12.0 (SAS Institute, Cary, NC, USA). The standard level of statistical significance was set at 5%.

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Conflict of interest: The authors declare that they have no conflicts of interest.

References

Aslam M, Vaezi MF (2013) Dysphagia in the elderly. Gastroenterol Hepatol 9: 784–795.

Bate A, Evans SJ (2009) Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf 18: 427–436.

Burstein ES, Ma J, Wong S, Gao Y, Pham E, Knapp AE, Nash NR, Olsson R, Davis RE, Hacksell U, Weiner DM, Brann MR (2005) Intrinsic efficacy of antipsychotics at human D2, D3, and D4 dopamine receptors: identification of the clozapine metabolite N-desmethylclozapine as a D2/D3 partial agonist. J Pharmacol Exp Ther 315: 1278–1287.

Carton L, Cottencin O, Lapeyre-Mestre M, Geoffroy PA, Favre J, Simon N, Bordet R, Rolland B (2015) Off-label prescribing of antipsychotics in adults, children and elderly individuals: A systematic review of recent prescription trends. Curr Pharm Des 21: 3280–3297.

Edwards IR, Aronson JK (2000) Adverse drug reactions: definitions, diagnosis, and management. Lancet 356: 1255–1259.

Dziewas R, Warnecke T, Schnabel M, Ritter M, Nabavi DG, Schilling M, Ringelstein EB, Reker T (2007) Neuroleptic-induced dysphagia: case report and literature review. Dysphagia 22: 63–67.

Furuta M, Yoshihisa Y (2013) Oral health and swallowing problems. Curr Phys Med Rehabil Rep 1: 216–222.

Gray JA, Roth BL (2007) The pipeline and future of drug development in schizophrenia. Mol Psychiatry 12: 904–922.

Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, Roth BL (2003) H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. Neuropsychopharmacology 28: 519–526.

Levey AI (1993) Immunological localization of m1-m5 muscarinic acetylcholine receptors in peripheral tissues and brain. Life Science 52: 441–448.

Linette LC, Peter RJ (2007) Medications used to treat psychosis. In: Ishiyaku Publishers, Inc.(ed.) Drugs and Dysphagia translated into Japanese by Kaneko Y and Doi T, Tokyo, p. 32–52.

Matsui M, Motomura D, Karasawa H, Fujikawa T, Jiang J, Komiya Y, Takahashi S, Taketo MM (2000) Multiple functional defects in peripheral autonomic organs in mice lacking muscarinic acetylcholine receptor gene for the M3 subtype. Proc Natl Acad Sci USA 97: 9579–9584.

Meiji Seika Pharma Co., Ltd. Tokyo (2018) Asenapine maleate (SYCREST®) Interview form.: http://www.info.pmda.go.jp/go/interview/1/780009_1179056F1021_1_1F (cited 9 June, 2018)

Miarons Font M, Rofes Salsench L (2017) Antipsychotic medication and oropharyngeal dysphagia: systematic review. Eur J Gastroenterol Hepatol 29: 1332–1339.

Nozaki S (2016) Medication and Dysphagia. J Jpn Soc Parenteral and Enteral Nutr 31: 699–704.

O'Neill JL, Remington TL (2003) Drug-induced esophageal injuries and dysphagia. Ann Pharmacother 37: 1675–1684.

Sakaeda T, Tamon A, Kadoyama K, Okuno Y (2013) Data mining of the public version of the FDA Adverse Event Reporting System. Int J Med Sci 10: 796–803.

Sekine Y, Rikihisa T, Ogata H, Echizen H, Arakawa Y (1999) Correlations between in vitro affinity of antipsychotics to various central neurotransmitter receptors and clinical incidence of their adverse drug reactions. Eur J Clin Pharmacol 55: 583–587.

Sliwa JA, Lis S (1993) Drug-induced dysphagia. Arch Phys Med Rehabil 74: 445–447.

Stewart JT (2003) Dysphagia associated with risperidone therapy. Dysphagia 18: 274–275.

Tokuda K (2006) Pharmacological action of antipsychotic drugs. Folia Pharmacol Japon 128: 173–176.