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Review article

Studies on constipation of psychiatry inpatients in Tottori Medical Center

Tsuruhei Sukegawa, Izumi Sakamoto[1] , Kiyoshi Doi[1], Yasuyuki Sakamoto[2], Toru Kashiwagi[*1]

[1] National Hospital Organization, Tottori Medical Center, Japan

[2] National Hospital Organization, Kamo Psychiatric Center, Japan

[*]Corresponding Author: Tsuruhei Sukegawa, National Hospital Organization, Tottori Medical Center, 876, Mitsu, Tottori-Shi, Tottori, 689-0203, Japan, Tel: +81-857-59-1111; Facsimile number: +81-857-59-1589; E-mail: sukegawt@tottri-iryo.hosp.go.jp

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Abstract

Psychiatric inpatients are likely to develop constipation and it is generally considered due to the adverse effect of psychotropic drugs. However, the analytical results of drug surveys in inpatients of Tottori Medical Center suggested that not only drugs but also treatment environment strongly influence constipation. If psychiatric treatment is administered at a lower dose in a free environment, it may be possible to improve abnormal autonomic nerve functions such as constipation.

Keywords: constipation, psychiatry, admission, psychotropic drugs, treatment environment

Introduction

Prescription survey in 2002

Constipation is induced by advanced age, lack of exercise, dietary restriction, and acetylcholine antagonists (anticholinergic drugs) [1-6]. Many psychiatric inpatients develop constipation and this is generally considered an adverse effect of psychotropic drugs such as anticholinergic and antipsychotic drugs [7]. Tottori Hospital (a hospital specialized in psychiatry which was integrated with Nishi Tottri Hospital and became the psychiatric department of Tottori Medical Center in 2005) performed a prescription survey on September 1, 2002 as an activity of the Ministry of Health, Labour and Welfare Fund for research on mental and nervous disorders '(13Shi-2) Studies on Clinical Features, Treatment, and Rehabilitation of Schizophrenia' [8]. This prescription survey was performed to investigate the actual state of high-dose polypharmacy administration of antipsychotic drugs. Based on the survey results of National Hospital Organization Tottori Medical Center (our hospital), the associations of the numbers of antipsychotic drugs and drugs for treatment of complication were analyzed. Significant association was noted in sex with regard to patient background and administration of 2 or more antiparkinson drugs (mainly anticholinergic drugs), 2 or more laxatives, and 3 or more antipsychotic drugs with regard to drugs (Table 1). These findings demonstrated the association of the number of antipsychotic drugs out of psychotropic drugs with the number of laxatives, i.e., antipsychotic drugs induce constipation, which is an easily acceptable result.

However, considering that the main action of antipsychotic drugs, dopamine receptor antagonism, is unlikely to be the cause of constipation, and antiparkinson drugs, which are used to treat parkinsonism induced by the anti-dopamine receptor action, cause constipation but the number of these drugs should have been adjusted because it was included in the model as an explanatory variable, a question arose whether polypharmacy of antipsychotic drugs is the only cause of massive laxative administration. Moreover, when the dose of antipsychotic drugs, which is a strong confounding factor of the number of antipsychotic drugs, was adjusted, significance of the association between the numbers of antipsychotic drugs and laxatives was lost, suggesting the association of low-potency antipsychotic drugs, which strongly influences the number of drugs but have only a small influence on the dose, i.e., although antipsychotic drugs have an anticholinergic action, it is not related to the dopamine receptor antagonism. Accordingly, the anticholinergic action is not exhibited by high-potency antipsychotic drugs exhibiting the action at a low dose whereas low-potency antipsychotic drugs readily exhibit the anticholiner-

gic action because these require a 50-100 times higher dose than that of high-potency antipsychotic drugs. Therefore, administration of low-potency antipsychotic drugs is more likely to be associated with laxative administration. Thus, we decided to proceed analysis of the relationship between the doses of antipsychotic drugs and laxatives. As a result, the treatment environments, such as quarantine, closed environment, and admission, were related to laxative administration. The details are described below.

Massive laxative administration and quarantine: Prescription survey in 2003

The relationship of massive laxative administration with patient background and the number or dose of other drugs administered was analyzed based on the prescription survey performed in 2003 [9]. The subjects were 252 inpatients. The mean age was 53.0 years old (standard deviation: 13.5 years old) and 105 patients (41.7%) were female. The sex, age, durations of this hospital stay and treatment, presence or absence of closed environment, quarantine, and restraint, and doses of antipsychotic drugs, high- and low-potency antipsychotic drugs, anticholinergic drugs, anti-anxiety drugs, and hypnotics at the time of September 1, 2003 were investigated as explanatory variables.

The results are shown in Table 2. The age, doses of antipsychotic drugs and low-potency antipsychotic drugs, administrations of prokinetic agents and pressors, and quarantine were selected as explanatory variables of massive laxative administration.

Prokinetic agents and laxatives may have been administered to treat constipation. Considering that prokinetic agents were additionally administered because control of constipation by massive laxative administration was insufficient, the associations of massive laxative administration and the number of prokinetic agents (>0) may have resulted from the same cause. Aging is known as a cause of constipation [1,2]. Constipation is an adverse effect of pressors. The number of pressors (>0) was selected as an explanatory variable of massive laxative administration even though the dose of low-potency antipsychotic drugs inducing orthostatic hypotension was adjusted, suggesting that constipation due to the adverse effect of pressors is not negligible. The dose of antipsychotic drugs (>535 mg CP) (chlorpromazine equivalent dose is presented as mg CP below) and the dose of low-potency antipsychotic drugs (> 89 mg CP) were selected as explanatory variables. Massive laxative administration could not be sufficiently explained with the dose of antipsychotic drugs, clarifying the presence of a stronger relationship between the dose of low-potency antipsychotic drugs and massive laxative administration. A point worthy of special mention is that 'quarantine' was selected as an explanatory variable in the same row with these. The relationship between lack of exercise and constipation has been mentioned for a long time [3], but it is clear that the autonomic nerve function of patients varies depending on how they are handled (treatment environment) and this was considered important.

Table 1. Relationship between the number of antipsychotic drugs and patient background†.

	Median	Adjusted OR						
		CP equivalent dose (mg/day) was adopted as a confounding factor				CP equivalent dose (mg/day) was excluded from confounding factors		
		OR	95% lower limit-upper limit	P		OR	95% lower limit-upper limit	P
Sex (male: 0, female: 1)	0	0.085	0.085-0.472	0.0002*		0.306	0.141-0.520	0.0016*
Age (years old)	52.7	—	—	—		—	—	—
Duration of hospital stay (years)	6.9	—	—	—		—	—	—
Duration of treatment (years)	23.3	—	—	—		1.843	0.933-3.640	0.0782
GAF	28	2.134	0.924-4.932	0.076		—	—	—
CP equivalent dose (mg/day)	775	14.916	5.840-38.100	<0.0001*		#	#	#
Antiparkinson drugs	1	3.348	1.339-8.374	0.0098*		3.27	1.484-7.207	0.0033*
Laxatives	1	1.759	0.785-3.939	0.1699		1.98	1.001-3.914	0.0496*
Hypnotics	1	—	—	—		—	—	—
Drugs for digestive organs excluding laxatives	0	—	—	—		—	—	—
Pressors	0	2.144	0.807-5.696	0.1262		—	—	—
Antianxiety drugs	0	—	—	—		—	—	—
Thymoleptics	0	—	—	—		—	—	—
Therapeutic drugs for diabetes	0	—	—	—		—	—	—
Others	0	—	—	—		—	—	—

†The relationship with the number of antipsychotic drugs (3 or more) was analyzed using multivariate logistic regression employing the stepwise method (αE=αD=0.2).
OR, Odds ratio; *, P<0.05; -, excluded from the model; #, not adopted in the multivariate model [8].

Table 2. Comparison between the group with massive laxative administration and control group (confounding factors were adjusted)†

Surveyed year	2003		
Explanatory variable	Odds ratio	95% lower limit-upper limit	P
Age (＞53.7 years old)	2.302	1.23-4.31	0.0092
With quarantine	2.736	1.20-6.24	0.0167
Number of prokinetic drugs (>0)	11.586	2.78-48.22	0.0008
Total dose of antipsychotic agents (>535 mg CP)	3.141	1.61-6.12	0.0008
Dose of low-potency antipsychotic drugs (>89 mg CP)	2.662	1.35-5.24	0.0046
Number of pressors (>0)	4.769	2.14-10.63	0.0001

†; Multivariate logistic regression analysis was performed regarding the presence or absence of massive laxative administration as a response variable and the other items as explanatory variables. Items with P>0.05 were excluded from the model.
mg CP, Chlorpromazine equivalent dose (mg) [9]

Treatment environment and laxatives: Prescription survey in 2004

Logistic regression analysis was performed regarding the treatment environment (open or closed) of 181 schizophrenia spectrum inpatients staying in the hospital on September 1, 2004 as a response variable and patient background and administered drugs as explanatory variables [10]. Ninety-two patients received environment in an open environment, males accounted for 66.3%, and the mean age was 53.5 (±10.4) years old. Eighty-nine patients received environment in a closed environment, males accounted for 51.7%, and the mean age was 49.0 (±14.6) years old. The duration of treatment at our hospital, number of diabetes treatment drugs, and dose of anticholinergic drugs were significantly related to the open environment, and the number of laxatives/prokinetic agents and total dose of psychotic drugs were significantly related to the closed environment (Table 3). Many patients in open wards were diabetic and this may have been due to a high degree of freedom in getting beverages and food because many patients stayed in hospital for a prolonged period and got familiar with inpatient treatment. The dose of anticholinergic drugs was high despite of the dose of antipsychotic drugs being low, but fewer laxatives/prokinetic agents were used.

When the correlation coefficient between variables related to the treatment environment was calculated (Table 4), a positive correlation was detected between the doses of anticholinergic drugs and antipsychotic drugs. However, novel antipsychotic drugs, multi-acting receptor targeted antipsychotics (MARTA), were significantly more frequently used in the closed environment. The novel antipsychotic drugs cause fewer extrapyramidal adverse effects, reducing the dose of anticholinergic drugs in many cases. Therefore, the dose of antipsychotic drugs was higher in the closed than open environment but drugs causing fewer extrapyramidal adverse effects, such as MARTA, were frequently used and this may have been one reason for the lower dose of anticholinergic drugs. Nevertheless, the number of laxatives/prokinetic agents was high in the closed environment, suggesting that it was directly due to the closed environment. Interestingly, diabetes is often problematic as an adverse effect of MARTA, but only a few diabetes treatment drugs were administered even though MARTA was frequently administered in closed wards because of strict management of beverages and food. It was clarified that the treatment environment is strongly related to complications of schizophrenia patients similarly to or more than prescriptions.

Comparison between in- and outpatients: Prescription survey in 2013

The subjects were 492 schizophrenia spectrum outpatients at the time of October 31, 2013, and 85 schizophrenia spectrum inpatients of our hospital at the time of September 1, 2013 [11]. In the previous studies, logistic regression analysis was employed for adjustment of confounding factors. When in- and outpatients were compared, the correlation coefficients of admission, the duration of hospital stay, massive administrations of antipsychotic drugs and laxatives were high (i.e., multicollinearity was strong), forming a single group. Thus, the matching method was employed in this analysis. Outpatients with a sex ratio, age, and dose of antipsychotic drugs matched to those in the 85 inpatients as much as possible were selected from the 492 outpatients, and the presence or absence of differences in patient background and administered drugs were analyzed. The outpatients selected by matching were regarded as adjusted for the

Table 3. Relationship between the treatment environment and patient background and drugs used (results of logistic regression analysis)

Explanatory variable	β	Standard error	χ^2value	p-value	Odds ratio	95%C.I. L.L.-U.L.
Duration of treatment at our hospital	-0.047	0.017	8.045	0.005	0.954	0.923-0.985
Number of laxatives/prokinetic agents	0.341	0.128	7.154	0.007	1.407	1.0.95-1.806
Number of diabetes treatment drugs	-1.376	0.628	4.801	0.028	0.253	0.074-0.865
Total dose of antipsychotic drugs	0.001	0.000	5.566	0.018	1.001	1.000-1.001
Dose of anticholinergic drugs	-0.296	0.105	7.940	0.005	0.744	0.605-0.914
Number of mood stabilizers	0.665	0.344	3.738	0.053	1.945	0.991-3.819

Table 4. Correlation coefficients of main variables related to the treatment environment

Variable	Treatment environment	Age	Duration of treatment at our hospital	Total dose of antipsychotic drugs	Dose of MARTA	Dose of anticholinergic drugs	Dose of antianxiety drugs/hypnotics	Number of mood stabilizers	Number of diabetes treatment drugs	Number of laxatives/prokinetic agents
Treatment environment (open=0, closed=1)	1	-0.178*	-0.184*	0.108	0.150*	-0.147*	0.152*	0.145	-0.158*	0.145
Age	-0.178*	1	0.571**	-0.127	-0.185*	-0.025	-0.278**	-0.175*	0.062	0.032
Duration of treatment at our hospital	-0.184*	0.571**	1	0.093	-0.119	0.114	-0.014	-0.059	0.017	0.224**
Total dose of antipsychotic drugs	0.108	-0.127	0.093	1	0.171*	0.346**	0.225**	-0.046	-0.097	0.070
Dose of MARTA	0.150*	-0.188*	-0.119	0.171*	1	-0.010	0.187*	-0.058	-0.088	0.031
Dose of anticholinergic drugs	-0.147*	-0.025	0.114	0.346**	-0.010	1	0.184*	0.019	-0.092	0.096
Dose of antianxiety drugs/hypnotics	0.152*	-0.278**	-0.14	0.225**	0.187*	0.184*	1	0.013	-0.063	0.281**
Number of mood stabilizers	0.145	-0.175*	-0.059	-0.046	-0.058	0.019	0.013	1	0.032	0.085
Number of diabetes treatment drugs	-0.158*	0.062	0.017	-0.097	-0.088	-0.092	-0.063	0.032	1	0.085
Number of laxatives/prokinetic agents	0.145	0.032	0.224**	0.070	0.031	0.096	0.281**	0.085	0.085	1

*：P<0.05 **：P<0.01

MARTA: multi-acting receptor targeted antipsychotics [10].

sex, age, and dose of antipsychotic drugs (adjusted outpatients).

As shown in Tables 5 and 6, only the numbers of laxatives/prokinetic agents (P<0.0002) and mood stabilizers (p<0.0179) were significantly different between the inpatients and adjusted outpatients. The high number of mood stabilizers may have been due to unstable psychiatric symptoms in the inpatients. When the Bonfferoni method was employed for adjustment in consideration that multiple comparison covered 19 items, the significance level was 0.00263, which suspended the significant difference in the number of mood stabilizers, and only the number of laxatives/prokinetic agents was significantly different between the inpatients and adjusted outpatients, suggesting that hospitalization is a direct cause of consti pation. However, if it is looked at critically, outpatients can purchase commercial laxatives. Therefore, further investigation is necessary.

Summary

Psychotropic drugs have been considered the cause of constipation in psychiatric inpatients. This is not a mistake, but the treatment environment was related to administration of laxatives and prokinetic agents at the same degree. In other words, constipation in psychiatric inpatients in our hospital may be largely due to the envir onment, such as quarantine and closed wards, and hospitalization itself.

Although prejudice decreased in the world compared with before, admission to a psychiatric hospital is very stressful for patients. Moreover, closed environments and quarantine limit freedom of behavior in daily life, which not only leads to a lack of exercise but also directly causes stress. It cannot be ruled out that the autonomic nervous system may become ataxic and induce constipation due to these conditions. The autonomic nerve function of psychiatric inpatients is impaired by mental disease, inpatient environment, and psychotropic drugs. Treatment with drugs at a low dose in a free environment may be important to maintain their autonomic nerve function.

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Conflicts of Interest

There is no conflict of interest related to this study.

Table 5. State of use of drugs to treat physical complications.

Drug	Adjusted outpatients (%)	Inpatients (%)	Odds Ratio	95%C.I.	*p* value*
Laxatives/prokinetic agents **	41 (48.2%)	65 (76.5%)	0.287	0.149－0.553	0.0002
Other digestive tract treatment drugs	16 (18.8%)	10 (11.8%)	1.739	0.740－4.090	0.2866
Diabetes treatment drugs	6 (7.1%)	2 (2.4%)	3.152	0.617－6.082	0.2772
Hypertension treatment drugs	10 (11.8%)	7 (8.2%)	1.486	0.538－4.106	0.6103
Hyperuricemia treatment drugs	2 (2.4%)	1 (1.2%)	2.024	0.180－2.753	0.4432
Hyperlipidemia treatment drugs	4 (4.7%)	5 (5.9%)	0.790	0.205－3.050	1.0000
Diuretics	0 (0%)	2 (2.4%)	0.000	－	0.4970
Circulatory system treatment drugs	0 (0%)	3 (3.5%)	0.000	－	0.2456
Hypotension treatment drugs	2 (2.4%)	7 (8.2%)	0.269	0.054－1.332	0.0570
Asthma treatment drugs	0 (0%)	1 (1.2%)	0.000	－	1.0000
Osteoporosis treatment drugs	0 (0%)	1 (1.2%)	0.000	－	1.0000

* Fisher's exact test was performed.

** Laxatives: Sennoside, Magnesium oxide, Pantethine, Glycerine enema.

Prokinetic drugs: Daikenchuto, Mosapride, Itopride [11].

Table 6. Comparison of psychotropic drugs between adjusted outpatients and inpatients

Drug	Adjusted outpatients	Inpatients	Z	P-value *
Number of antipsychotic drugs administered (number/day/patient)	1.96 (0.85)	1.69 (0.91)	0.0900	0.9283
Dose of antipsychotic drugs (mg/day/patient)	639 (403)	699 (427)	1.1864	0.2354
Number of anticholinergic drugs administered (number/day/patient)	0.66 (0.56)	0.53 (0.544)	1.4838	0.1379
Dose of anticholinergic drugs (mg/day/patient)	1.75 (1.78)	1.42 (1.78)	1.3724	0.1699
Number of antianxiety drugs/hypnotics (number/day/patient)	0.95 (0.89)	0.82 (0.74)	0.8489	0.3960
Dose of antianxiety drugs/hypnotics (mg/day/patient)	10.59 (16.10)	9.06 (12.39)	0.3385	0.7350
Number of mood stabilizers (number/day/patient)	0.24 (0.50)	0.39 (0.51)	2.3687	0.0179

The values in each group are presented as the means (standard deviation).
*: Normalization test of the Mann-Whitney U-test was employed [11].

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