

patient), with delirium during the final two weeks of life (based on a retrospective chart review and using Diagnostic and Statistical Manual of Mental Disorders, 4 (DSM-IV) criteria<sup>15</sup>), 2) capable of replying to a self-reported questionnaire, 3) aware of the diagnosis of malignancy, and 4) no serious psychological distress recognized by the primary palliative care physicians. The last criterion was adopted in the same way as in our previous surveys,<sup>16,17</sup> on the assumption that primary palliative care physicians could identify families who would suffer serious psychological distress from this survey, because they were closely involved in caring for their relative in an inpatient care setting with a mean admission period of 43 days. We excluded patients with preexisting symptomatic organic brain pathology (i.e., brain metastasis, infarction) or psychiatric disorders other than delirium (i.e., psychosis, dementia), because the psychiatric symptoms might influence the results. To minimize the possibility of sampling bias among institutions, we compared the percentages of patients diagnosed with delirium per all dead patients and the percentages of patients excluded from this study due to the last criterion among the institutions.

Each hospital was requested to consecutively enroll the families of 90 patients who developed delirium and died in 2005 (one institution with clinical activity of less than one year enrolled all patients treated there).

The completion and return of the questionnaire was regarded as consent to participate in this study. Ethical and scientific validity was confirmed by the institutional review board of each hospital.

### *Measurement Tools*

**Questionnaire.** A questionnaire (available from the authors upon request) was developed for this study based on a systematic literature review,<sup>6-14,18-23</sup> our previous qualitative study based on in-depth interviews with 20 bereaved family members,<sup>14</sup> and discussions among the authors. Content validity was assessed by full agreement of the authors, and the face validity of the questionnaire was confirmed by a pilot test.

As background data, the families reported their ages, genders, relationships to the patient, and intervals from patient death to the study. In the first part of the questionnaire,

we asked the respondents whether they thought the patient was delirious or not, because in our previous interview study, 17 of 37 families denied delirium despite diagnostic confirmation based on chart review.<sup>14</sup> Delirium was paraphrased in the questionnaire as "the rapid development of difficulty in concentration, forgetfulness, disorientation about time and place, hallucinations and delusions, incoherent speech, clouding of consciousness and difficulty in communicating, emotional instability, reversal of daytime and nighttime activities (drowsiness during the day and wakefulness during the night), and inconsistent behavior, with these conditions changing even within a day." We carefully developed this introduction section on the basis of the DSM-IV criteria through full agreement among the author liaison psychiatrists and palliative care specialists.

The primary endpoints of this study were family-perceived emotional distress related to terminal delirium and the necessity for improvement in professional care at that time. Due to the lack of validated instruments, these outcome parameters were developed for this study following previous surveys.<sup>16,17</sup> The level of family-perceived distress was evaluated by the response to "How distressing was the patient's delirium for you?," rated on a 5-point scale from 1, "no distress at all" to 5, "very distressing." The necessity for improvement was evaluated by the answer to "How much improvement do you think is necessary in the care for delirium?," rated on a 4-point scale as 1, "no need for improvement," 2, "need for some improvement," 3, "need for considerable improvement," and 4, "need for much improvement." To explore the families' emotions, we asked the respondents to rate their degree of agreement with 16 statements to describe their feelings on a 5-point Likert-type scale of 1, "disagree," to 5, "strongly agree" (Table 2). In addition, we asked the respondents to rate their degree of agreement with eight potential meanings of delirium for the family member on a 5-point Likert-type scale of 1, "disagree," to 5, "strongly agree" (Table 4).

The families were further requested to report factors potentially contributing to these primary endpoints. They were conceptualized prior to the survey and classified into the

following categories: 1) family-reported patient behavior (rated on a 5-point Likert-type scale of 1: none, 2: occasionally, and 3: often) (Table 3); 2) families' interpretation of the causes of delirium (examined by the degree of agreement on a 5-point Likert-type scale of 1: disagree to 5: strongly agree) (Table 4); 3) family-reported professional care practice (examined using the yes-no format) (Table 5); and 4) the family care subscale of the Care Evaluation Scale.<sup>24</sup>

The Care Evaluation Scale is an originally validated 28-item questionnaire to measure bereaved family-perceived necessity of improvement in end-of-life care;<sup>24</sup> its reliability and validity have been well established. The family care subscale was designed to quantify the family-perceived necessity of improvement in care to relieve the family care burden. A lower score indicated a greater need for improvement (possible range, 0–10).

**Chart Review Data.** Primary palliative care physicians recorded the patient backgrounds (age, gender, primary tumor site, admission periods, and the type and severity of delirium on item 9 of the Memorial Delirium Assessment Scale—Japanese version<sup>25</sup>).

#### Analyses

To describe the estimated frequency of the phenomenon observed, we calculated the 95% confidence intervals (CI) for each figure.

For comparisons, the respondents were classified into two groups: family members who rated their distress level as "very distressed" (high-level distress) and others (low-level distress); and family members who rated the necessity for improvement as "much," "considerable," or "some" (defined as a high level of perceived necessity for improvement) and others (low level). These cutoff points were determined on the basis of the actual data distribution to divide the whole sample into appropriate sizes of comparison groups.

To explore the underlying structure of the families' emotions (Table 2), we reported factor-loading values by exploratory factor analysis with promax rotation on emotion-related items, and calculated Cronbach's alpha. Two ambivalent items with different meanings within one sentence were excluded from this analysis.

To explore the determinants of the levels of family-perceived distress and necessity for improvement, we initially screened: 1) demographic variables (patient age, gender, admission periods, responding family member age, gender, relationship to the patient, interval from patient death to study, health status in the last week, availability of someone with whom they could consult about the patient, and someone who could care for the patient instead of them); 2) type and severity of delirium (measured using item 9 of the Memorial Delirium Assessment Scale by the primary physicians); 3) family-reported patient behavior (Table 3); 4) families' interpretation of the causes of delirium (Table 4); 5) family-reported professional care practice (Table 5); and 6) the family care subscale of the Care Evaluation Scale. Univariate analyses were performed using Student's *t*-test or the Chi-square test, where appropriate. Multiple logistic regression analyses were then performed in a forward-elimination fashion. All potential predictors with statistical significance by univariate analyses were entered in the equation as independent variables, and we reported the factors that achieved  $P < 0.1$  because they had a clinically meaningful interpretation despite marginal statistical significance.

All analyses were performed using the Statistical Package for the Social Sciences (version 11.0).

#### Results

Of 984 patients who died during this study period, 672 patients (68%) were diagnosed with delirium during the final two weeks of life. Of them, 53 patients had preexisting symptomatic organic brain or psychiatric disorders, and 19 patients had no competent adult family members available. Of the remaining 600 patients, we excluded 40 bereaved family members (6.7%) due to serious psychological distress recognized by primary physicians. Among the institutions, the percentages of patients diagnosed with delirium per all deceased patients ranged from 47% to 87% (three institutions below 70%), and the percentages of patients excluded from this study due to psychological reasons ranged from 0% to 12% (all but one institution below 7.0%).

We thus sent questionnaires to 560 families, 10 of which were returned as undeliverable. Four hundred twenty-seven families returned questionnaires (response rate, 78%, 427/550). Of them, nine families refused to participate, and 16 responses were excluded due to missing data in primary endpoints. Thus, we obtained 402 effective responses (effective response rate, 73%, 402/550). As 160 families denied delirium episodes, further analyses were performed on 242 responses. Table 1 summarizes the backgrounds of patients and bereaved family members. The subtypes of delirium were hypoactive, 29% ( $n = 70$ ); hyperactive, 48% ( $n = 117$ ); and mixed, 20% ( $n = 48$ ). Symptom severity was mild, 39% ( $n = 95$ ); moderate, 47% ( $n = 114$ ); and severe, 11% ( $n = 26$ ) on item 9 of the Memorial Delirium Assessment Scale.

#### *Overall Levels of Family-Reported Distress and Necessity for Improvement*

The degree of family-reported distress was very distressing (32% [95% CI: 26,38],  $n = 77$ ), distressing (22% [95% CI: 17,28],  $n = 53$ ), slightly distressing (31% [95% CI: 25,37],  $n = 74$ ), not so distressing (10% [95% CI: 7.0,15],  $n = 25$ ), and not distressing at all (5.4% [95% CI: 3.0-9.0],  $n = 13$ ). The necessity of improvement in delirium care as rated by the family members was much improvement needed (0.8% [95% CI: 0,3.0],  $n = 2$ ), considerable improvement needed (5.0% [95% CI: 3.0,9.0],  $n = 12$ ), some improvement needed (31% [95% CI: 25,37],  $n = 75$ ), and no improvement needed (59% [95% CI: 53,65],  $n = 143$ ).

#### *Family-Reported Emotions*

Exploratory factor analysis categorized family-reported emotions into seven categories: ambivalent, guilt and self-blame, worry about staying with the patient, burden about proxy judgment, burden to others, acceptance, helplessness, and relief. More than half of the respondents had ambivalent wishes, guilt and self-blame, and worries about staying with the patient. One-fourth to one-third reported that they felt a burden over proxy judgments, burden to others, acceptance, and helplessness. Less than 5% reported positive feelings such as relief (Table 2).

Table 1  
Backgrounds

	% (n)
Patients	
Age (mean $\pm$ SD)	69 $\pm$ 12
Sex	
Male	64 (155)
Female	36 (87)
Primary sites	
Lung	26 (62)
Stomach	13 (31)
Colon, rectum	11 (27)
Pancreas, bile duct	12 (29)
Liver	5.3 (13)
Neck	6.2 (15)
Uterus, ovary	4.1 (10)
Bladder, kidney, prostate	7.9 (19)
Breast	3.3 (8)
Esophagus	2.5 (6)
Unknown	2.1 (5)
Others	7.0 (17)
Admission periods (d) (mean $\pm$ SD)	43 $\pm$ 48 (median, 28)
Bereaved families	
Age (mean $\pm$ SD)	58 $\pm$ 13
Sex	
Male	25 (60)
Female	74 (178)
Relationship	
Spouse	55 (132)
Child	30 (72)
Parents	1.7 (4)
Siblings	4.1 (10)
Others	9.1 (22)
Interval from patient death (mo) (mean $\pm$ SD)	12 $\pm$ 13 (median, 11)
In the last week	
Health status	
Good	74 (180)
Poor	24 (58)
Availability of person with whom the respondent consulted	91 (221)
about the patient	
Availability of person who cared for the patient instead of the respondent	71 (171)
Frequency of staying with the patient	
Every day	77 (186)
4-6 days/wk	12 (29)
1-3 days/wk	8.7 (21)

Some data do not add up to 100% due to missing values.

#### *Family-Reported Patient Behavior*

The bereaved family members reported various patient behaviors other than "psychiatric symptoms." More than half of the respondents reported that, during the delirium episodes, the patient expressed physiologic desires, seemed incoherent but talked about actual past events, and talked about uncompleted life tasks. In addition, about 30% said that the patient apologized

Table 2  
Family-Reported Emotions

	Agree or Strongly Agree	95% CI	Factor Loadings	Alpha
	% (n)			
<i>Ambivalent</i>				N.C.
Simultaneously wanted the patient both to stay awake and to relieve the patient from suffering.	64 (155)	58,70	N.C.	
Simultaneously wanted the patient both to live longer and to die without suffering.	40 (97)	34,46	N.C.	
<i>Guilt and self-blame</i>				0.87
Could not understand what the patient wished for.	62 (149)	55,68	0.89	
Might not be able to realize the patient's unfulfilled wishes.	56 (135)	49,62	0.89	
Guilty, could not do enough for the patient.	52 (126)	46,58	0.88	
<i>Worry about staying with the patient</i>				0.77
Worried about caring the patient alone.	58 (140)	51,64	0.89	
Anxious about taking their eyes off the patient.	57 (139)	51,64	0.88	
<i>Burden about proxy judgment</i>				N.C.
Burden about having to make a decision on behalf of the patient.	39 (94)	33,45	0.86	
<i>Burden to others</i>				0.60
Distressed as the patient troubled others.	38 (91)	32,44	0.68	
Not wanting other members of the family to see the patient.	35 (84)	29,41	0.69	
Sad to see the patient having completely changed.	29 (71)	24,35	0.85	
<i>Acceptance</i>				N.C.
Just accepting the fact.	35 (84)	29,41	0.96	
<i>Helplessness</i>				0.78
Helplessness about what to do.	32 (78)	27,38	0.87	
Not sure about what was happening.	28 (68)	23,34	0.91	
<i>Relief</i>				0.81
Felt relieved.	3.3 (8)	2.0,6.0	0.89	
Felt happy.	2.5 (6)	1.0,5.0	0.91	

N.C. = not calculated.

for past events and was distressed as they noticed that they were talking strangely. About 20% of the family members reported a transcendent experience, that is, that the patient talked to or met people who had died (Table 3).

#### *Family-Perceived Meaning of Delirium and Interpretation of the Causes of Delirium*

About half of the respondents perceived delirium as a sign of approaching death, the patient trying to express what to say, or patient suffering. About one-fourth to one-third perceived delirium as a natural part of the dying process, dreaming, a transcendent phenomenon (entering the after-death world), or relief from actual suffering. Forty to 60% of the families interpreted the causes of delirium as pain/physical discomfort or medication effects (Table 4).

#### *Family-Reported Professional Care Practice for Delirium*

The families generally reported high adherence to the recommended care practice for

terminal delirium. Eighty percent or more families agreed that professionals treated patients the same as before, tried to understand what the patient wanted to say, were sufficiently compassionate to the family, explained the expected course along with daily changes, and respected the patient's subjective world (Table 5).

#### *Determinants of Family-Perceived Emotional Distress and Necessity of Improvement*

Compared with the family members with low-level distress, family members with high-level distress were more likely to experience agitated behavior, incoherent speech, the patient talking about uncompleted life tasks, the patient appearing incoherent but talking about actual past events, and being distressed by noticing that they were talking strangely; more likely to interpret the causes of delirium as pain/physical discomfort, medication effects, psychosis/"getting crazy," and mental weakness/death anxiety; less likely to report

Table 3  
Family-Reported Patient Behavior in the Delirium Episodes

	Occasionally	95% CI	Often	95% CI
	% (n)		% (n)	
<i>"Psychiatric symptoms"</i>				
Incoherent speech	53 (128)	47, 59	25 (60)	20, 31
Mentally clear in some situations within the day	36 (88)	31, 43	37 (89)	31, 43
Hallucinations	34 (83)	29, 41	17 (40)	12, 22
Agitated behavior	31 (75)	25, 37	15 (36)	11, 20
<i>Other than "psychiatric symptoms"</i>				
Expressed physiologic desires (excretion, thirst)	31 (76)	26, 38	40 (96)	34, 46
Seemed incoherent but talked about actual past events	41 (100)	35, 48	26 (62)	20, 32
Talked about uncompleted life tasks	32 (78)	27, 38	24 (57)	19, 29
Good mood	33 (80)	27, 39	7.4 (18)	5.0, 11
Apologized for past events	22 (53)	17, 28	6.6 (16)	4.0, 11
Distressed as the patient noticed him/herself talking strangely	21 (51)	16, 27	6.6 (16)	4.0, 11
Said that the patient talked to or met people who had died	18 (44)	14, 24	4.1 (10)	2.0, 7.0

the medical professionals as present with the family; and more likely to report the patient being physically restrained (Table 6).

Compared with the family members who perceived a low-level necessity of improvement, family members who perceived a high-level necessity of improvement were more likely to be young and male; more likely to interpret the causes of delirium as pain/physical discomfort and medication effects; less likely to report that the medical professionals were present with the family, respected the patient's subjective world, explained the expected course along with daily changes, tried to understand what the patient wanted to say, were sufficiently compassionate to the family, had facilitated communication before it became

difficult, and had confirmed the patient's wishes before communication become difficult; and reported a lower score of the family care subscale of the Care Evaluation Scale.

Multiple logistic regression analyses revealed that the independent determinants of high-level distress or high-level necessity of improvement were younger age; male gender; experience of agitation and incoherent speech; interpretation of the causes of delirium as pain/

Table 4  
Family-Perceived Meaning of Delirium and Interpretations About the Causes of Delirium

	Agree, or Strongly Agree		95% CI
	% (n)		
<i>Meaning of delirium</i>			
Sign of approaching death	59 (143)	53, 65	
Trying to express what the patient wanted to do or say	52 (125)	45, 58	
Suffering	45 (108)	38, 51	
A natural part of the dying process	31 (74)	25, 37	
Dream	25 (61)	20, 31	
Entering after-death world	22 (54)	17, 28	
Relief from actual suffering	22 (53)	17, 28	
Happy and welcome experience	7.0 (17)	4.0, 11	
<i>Interpretation about the causes of delirium</i>			
Pain or physical discomfort	60 (144)	53, 66	
Medication effects	41 (99)	35, 47	
Psychosis or "becoming crazy"	19 (46)	15, 24	
Mental weakness or death anxiety	15 (37)	11, 20	

Table 5  
Family-Reported Professional Care Practice for Delirium

	Practiced	95% CI
	% (n)	
Treated patients the same as before	94 (227)	90, 96
Tried to understand what the patient wanted to say	88 (214)	84, 92
Was sufficiently compassionate to the family	86 (208)	81, 90
Explained the expected course along with daily changes	86 (207)	80, 89
Respected the patient's subjective world without denying "incoherent things"	83 (202)	78, 88
Discussed with the family about how to deal with the issue	75 (181)	69, 80
Explained the pathology of delirium (not dementia or psychosis)	72 (175)	66, 78
Was present with the family	71 (173)	65, 77
Facilitated with family members in communicating and being with the patient before it became difficult	68 (164)	62, 73
Explained the universality of delirium	66 (159)	59, 71
Confirmed the patient's wishes before communication became difficult	54 (131)	48, 60
<i>Physical restraint</i>		
Before admission to palliative care units	3.3 (8)	2.0, 6.0
In palliative care units	2.5 (6)	1.0, 5.0

physical discomfort, medication effects, or mental weakness/death anxiety; and medical staff being present with the family, respecting the patient's subjective world, explaining the expected course along with daily changes, and relieving the family care burden.

### Discussion

This is, to our knowledge, the first systemic survey to investigate the potential correlations of the distress levels of families and the perceived necessity of improvement in care related to terminal delirium with family-reported professional care practice, family-reported patient behavior, and perception of the causes of delirium.

This survey revealed that, although a relatively small number of families (5.8%) reported that considerable or much improvement was necessary in the professional care they had received in certified palliative care units, about half of the families reported being very distressed or distressed about the experience of terminal delirium. This figure is relatively low compared with the previous two surveys,<sup>6,7</sup> but confirms that at least 50% of the families of patients with delirium experienced considerable emotional distress.

The most important finding of this study was the identification of factors associated with the distress levels of families and their perceived necessity of improvement. The chief factors included family experience of agitation, their interpretation of the causes of delirium, and their perception about the care they had received.

Consistent with previous surveys that identified agitation as a significant determinant of family distress,<sup>6,7</sup> family-reported agitation was an important determinant of family distress in this study. The control of agitation symptoms, therefore, is an important task for palliative care clinicians. This study revealed, however, that ambivalent wishes between symptom control and maintaining communication were the most common emotions of the families. Together with qualitative studies stressing the importance of ambivalent wishes in this situation,<sup>12,14</sup> clinicians should note that families want not only symptom palliation but also much broader elements of quality of life, such as maintaining cognitive control,

communicating with others, and living as long as possible.<sup>26,27</sup> That is, clinically, pharmacologically sedative therapy should not be routinely applied to control agitation symptoms without careful individualized considerations, and the depth or duration of sedation should be closely adjusted for each situation.<sup>28</sup>

Families often interpreted delirium as the consequences of pain/physical discomfort, medication effects, psychosis/"becoming crazy," or mental weakness/death anxiety, and these interpretations were significantly associated with both family distress and necessity of improvement. These findings confirm the great importance of information focusing on the cause and pathologies of delirium (i.e., terminal delirium is usually not an expression of pain, medication effects, "becoming crazy," or mental weakness), as stated in expert literature.<sup>10,14</sup>

The major care practices related to a family's emotional distress and necessity of improvement included being present with the family, respecting the patient's subjective world, explaining the expected course with daily changes, and relieving the family care burden.

Of special note, as this study suggests, respecting the patient's subjective world can be an important care strategy in terminal delirium. This care strategy was associated with the overall necessity of improvement, and the family members experienced various patient behaviors other than "psychiatric symptoms": the patient expressed physiologic desires, seemed incoherent but talked about actual past events, talked about uncompleted life tasks, and apologized for past events. Consistent with the recommendations of palliative care textbooks,<sup>8-11</sup> these findings suggest that the care strategy for terminal delirium may include exploring and fulfilling unmet physiological needs behind delirium symptoms, and trying to understand the "strange" behavior of delirious patients as a potentially meaningful experience to find a clue for important landmark events and achieve uncompleted life tasks for patients and families.

Among care strategies investigated in this study, only being with the patient was associated with families' emotional distress. This result indicates, as nonempirical literature stresses the importance of "being" for palliative care clinicians,<sup>8-11</sup> being with the families of delirious patients is an essential element of care.

Table 6  
Determinants of Family-Reported Emotional Distress and Necessity of Improvement

	Emotional Distress Level				Necessity of Improvement			
	Univariate Analyses		Multivariate Analysis <sup>a</sup>		Univariate Analyses		Multivariate Analysis <sup>b</sup>	
	High-Distress (n = 77)	Low-Distress (n = 165)	Odds Ratio [95% CI]	P	High Necessity (n = 89)	Low Necessity (n = 143)	Odds Ratio [95% CI]	P
<i>Background</i>								
Age (family)					55 ± 11	60 ± 14 <sup>c</sup>	0.96 [0.93–0.99]	0.016
Sex (family, female)					64% (n = 57)	79% (n = 113) <sup>c</sup>	0.22 [0.096–0.50]	0.001
Sex (patient, female)					45% (n = 40)	31% (n = 44) <sup>c</sup>		
<i>Family-reported patient behavior<sup>d</sup></i>								
Agitated behavior	0.85 ± 0.78	0.51 ± 0.69 <sup>e</sup>	1.5 [0.98–2.4]	0.063				
Incoherent speech	1.2 ± 0.72	0.97 ± 0.64 <sup>f</sup>	1.7 [1.0–2.9]	0.042				
Talked about uncompleted life tasks	1.0 ± 0.83	0.73 ± 0.77 <sup>f</sup>						
Seemed incoherent but talked about actual past events	1.2 ± 0.72	0.90 ± 0.76 <sup>e</sup>						
Distressed as the patient noticed	0.49 ± 0.73	0.30 ± 0.53 <sup>e</sup>						
<i>Interpretations of the causes<sup>e</sup></i>								
Pain or physical discomfort	3.0 ± 1.3	2.5 ± 1.2 <sup>f</sup>	1.3 [0.95–1.7]	0.099	2.9 ± 1.2	2.5 ± 1.2 <sup>e</sup>		
Medication effects	2.3 ± 1.2	2.0 ± 1.2 <sup>e</sup>			2.4 ± 1.1	1.9 ± 1.200 <sup>f</sup>	1.5 [1.1–2.1]	0.014
Mental weakness or death anxiety	1.6 ± 1.3	1.3 ± 0.94 <sup>e</sup>	1.3 [0.97–1.8]	0.078				
Psychosis or "getting crazy"	1.6 ± 1.3	1.3 ± 1.1 <sup>e</sup>						
<i>Family-reported professional care<sup>a</sup></i>								
Was present with the family	62% (n = 48)	76% (n = 125) <sup>e</sup>	0.49 [0.23–1.0]	0.068	58% (n = 52)	83% (n = 119) <sup>e</sup>	0.35 [0.12–1.0]	0.053
Respected the patient's subjective world					81% (n = 72)	88% (n = 126) <sup>e</sup>	0.16 [0.019–1.3]	0.088
Explained the expected course					79% (n = 70)	92% (n = 132) <sup>f</sup>	0.13 [0.028–0.64]	0.011
Tried to understand what the patient said					87% (n = 77)	93% (n = 133) <sup>e</sup>		
Was sufficiently compassionate to the family					76% (n = 68)	93% (n = 133) <sup>e</sup>		
Had confirmed the patient's wishes before communication became difficult					44% (n = 39)	64% (n = 91) <sup>e</sup>		

(Continued)

Table 6 (Continued)

	Emotional Distress Level			Necessity of Improvement		
	Univariate Analyses		Multivariate Analysis <sup>a</sup>	Univariate Analyses		Multivariate Analysis <sup>b</sup>
	High-Distress (n = 77)	Low-Distress (n = 165)	Odds Ratio [95% CI]	High Necessity (n = 89)	Low Necessity (n = 143)	Odds Ratio [95% CI]
Had facilitated communication before it became difficult				62% (n = 55)	73% (n = 105) <sup>c</sup>	
Relieved the family care burden <sup>d</sup>				6.4 ± 2.5	7.9 ± 2.5 <sup>e</sup>	0.84 [0.73–0.98]
Physical restraint	10% (n = 8)	3.6% (n = 6) <sup>f</sup>				0.025

<sup>a</sup>R<sup>2</sup> = 0.15.<sup>b</sup>R<sup>2</sup> = 0.37.<sup>c</sup>P < 0.05.<sup>d</sup>Rated as 0 (none), 1 (occasionally), and 2 (often).<sup>e</sup>P < 0.001.<sup>f</sup>P < 0.01.<sup>g</sup>Rated as 0 (strongly disagree) to 4 (strongly agree).<sup>h</sup>Rated as practiced or not.<sup>i</sup>Rated on the family care subscale of the Care Evaluation Questionnaire. Lower score indicates a family-perceived higher necessity of care to relieve the family care burden.

The family-perceived necessity of improvement in care to relieve the family care burden was a significant determinant in the overall family-perceived necessity of improvement. As the family is an important target in palliative care, clinicians should make maximum efforts to relieve the family care burden, through reassuring the families that they can leave the patients' care to the staff, making the hospital environment comfortable for the families, and coordinating support from other members of the family.

Of interest was that this study highlighted some specific emotions evoked by the experience of terminal delirium. In this study sample, the three major emotions were ambivalent wishes, guilt and self-blame, and worry about staying with the patient. As only a few qualitative studies proposed a care strategy to relieve such specific distress,<sup>14</sup> more empirical studies are needed to understand in-depth family emotions related to terminal delirium and explore a specific care strategy.

Despite several strengths, including the success in obtaining a large sample with more than a 70% response rate, this study has some limitations. First, due to its retrospective nature, there might be a recall bias. Second, some families denied the episode of delirium despite a psychiatrically confirmed diagnosis, and might recall episodes other than delirium. Third, as all patients received specialized palliative care, adherence levels to recommended care practice were generally high and might result in low-sensitivity statistical analyses, and the findings could not be automatically generalized to other situations. Fourth, the cross-sectional design of this study cannot allow the causality of the associations identified. Fifth, we excluded 6.7% of the potential respondents with profound emotional distress due to ethical reasons. Finally, what is important for a good death, such as maintaining consciousness and dying during sleep, is different among cultural backgrounds,<sup>27,28</sup> and the results might not be automatically applied to different cultural settings.

In conclusion, a considerable number of family members experienced high levels of emotional distress and felt some need for improvement of the care for terminal delirium. Control of agitation symptoms with careful consideration of ambivalent family wishes,



information about the pathophysiology of delirium, being present with the family, respecting the patient's subjective world, explaining the expected course with daily changes, and relieving the family care burden can be useful care strategies. Intervention trials to determine the efficacy of these care strategies are needed.

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SC route intermittently, without the problems of skin irritation, by flushing the solution through with hypodermoclysis. Prospective trials are needed to further investigate these observations. Thus far, we have had experience with 18 patients given SC methadone using this method, all achieving adequate pain control, without additional morbidity arising from the infusion site. This allows physicians more flexibility with regard to the use of methadone. It will provide patients with more options for effective pain management, even in the terminal phase of their lives. This is of particular importance in patients who, by virtue of decreased level of consciousness in the terminal phase of illness, can no longer continue on oral methadone, and in whom the rectal route of administration proves difficult or invasive.

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## First Panic Attack Episodes in Head and Neck Cancer Patients Who Have Undergone Radical Neck Surgery

To the Editor:

Panic disorders or panic attacks in cancer patients are not well understood. Derogatis et al. found that only 2% of randomly surveyed cancer patients had anxiety disorders and that none of these disorders were related to panic.<sup>1</sup> However, physicians must often treat patients who have experienced clinically significant panic attacks in clinical oncology settings; such patients must receive immediate treatment, as marked fear could lead to a discontinuation of cancer treatment.<sup>2</sup> Panic attacks can occur in the context of several medical conditions (e.g., cardiac, respiratory, vestibular, or gastrointestinal disorders),<sup>3</sup> and certain types of cancer patients may be at risk for panic attacks.

We treated two cases who experienced radical panic attack episodes after undergoing radical head and neck surgery. In both cases, the occurrence of panic attack symptoms were notable, and pain, which sometimes occurs after radical neck surgery,<sup>4-6</sup> seemed to contribute to the panic attacks. As the panic attacks were recognized immediately, the attacks were successfully treated using both psychological and pharmacological interventions. To the best of our knowledge, this is the first report

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concerning panic attacks in patients who have undergone radical neck surgery, and who might have an increased risk of panic attacks.

### Case 1

Ms. A. was a 44-year-old woman who was hospitalized in the Head and Neck Surgery unit to undergo surgery for hypopharyngeal cancer (T4a N2b M0, Stage IVA). On admission, she had normal concerns about the surgery, and her case was not remarkable in any way. She was a homemaker and had three children. She had no past history of psychiatric disorder, including panic attack, and no family history of major psychiatric illness.

She underwent a total pharyngolaryngoesophagectomy, bilateral neck dissection, and a free jejunum transfer for a pharyngoesophageal reconstruction. Two days after her operation, she felt a gradually increasing stiffness in her neck and expressed great concern about this symptom. Three days after her operation, she began screaming, "I am being strangled!! I am dying!!" and had a terrified facial expression. Her attending physician performed a physical examination but observed no unusual findings, including the postoperative wound. The patient's degree of oxygen saturation was normal. Laboratory tests revealed anemia, hypoalbuminemia, liver dysfunction, and an inflammatory reaction, but these findings were consistent with the usual postoperative state. A psychiatric problem was suspected, and the patient was referred to the psychiatric division.

A psychiatric evaluation revealed that her consciousness was clear and that her major complaint was neck stiffness. She complained that the degree of stiffness would suddenly increase and that she felt an intense fear of death from strangulation. She had concomitant symptoms of palpitation, sweating, sensations of shortness of breath, feeling of choking, and simultaneous fear of losing control, and her episodes met the DSM-IV-TR criteria for a panic attack. Such episodes would cease after a few minutes but occurred repetitively. She never felt at ease and was afraid of her next attack.

We informed the patient that her vital signs were normal and that there was no threat to her life. We explained that an autonomic imbalance arising from anxiety was the cause of her attacks, promised relief from her

symptoms, and showed her how to perform diaphragmatic breathing. We also administered a bolus injection of diazepam (5 mg) and a continuous intravenous injection of diazepam (10 mg/day) and clomipramine (12.5 mg/day). Her symptoms improved immediately after the diazepam injection, and the intensity and frequency of her attacks decreased gradually. Seven days after surgery, her attacks had completely disappeared, and her anticipatory fear of attacks had also disappeared, although the administration of psychotropic agents was stopped 10 days after her surgery. A tolerable degree of mild neck stiffness continued after the cessation of the panic attacks. She was discharged from hospital 25 days after surgery.

### Case 2

Mr. B. was a 53-year-old man who was hospitalized in the Head and Neck Surgery unit to undergo surgery for oropharyngeal cancer (T3 N2b M0, Stage IVA). On admission, he was extremely worried about the surgery and appeared agitated and uncomfortable; consequently, he was referred to the psychiatric division and was diagnosed as having an adjustment disorder with anxiety. He was treated with alprazolam (0.8 mg/day) until the day before his surgery, and his symptoms disappeared. He had no other history of psychiatric disorder, including panic attack, and he had no family history of major psychiatric illness.

The patient underwent a total glossectomy with a total laryngectomy, bilateral neck dissection, and a rectus abdominis free flap transfer for pharyngeal reconstruction. After the operation, he felt a gradually increasing stiffness in his neck. Seven days after his operation, he became extremely agitated and could not stay in bed. He stood up and began to walk around with a very upset appearance. As a peripheral venous line and a surgical drain had been inserted, the patient was in danger of pulling out the line and drain. Consequently, the nurse made an emergency call to the attending physician and psychiatrist. No unusual findings were found, including the postoperative wound, the degree of oxygen saturation, and laboratory tests.

A psychiatric evaluation revealed that his consciousness was clear and that his major complaint was very severe neck stiffness of a degree that varied widely and immediately from

tolerable to extremely severe, leading to fear of death. He had concomitant symptoms of palpitation, sensation of shortness of breath, feeling of choking, and simultaneous fear of losing control, and his episodes met the DSM-IV-TR criteria for a panic attack. When such an attack occurred, he was unable to remain still because of extreme fear, and psychiatric symptom management was urgently required.

We informed the patient that his vital signs were normal and that there was no threat to his life. We explained that an autonomic imbalance arising from anxiety was the cause of his attacks, promised relief from his symptoms, and showed him how to perform diaphragmatic breathing. After the intravenous bolus injection of diazepam (5 mg), his panic attack temporarily improved, but he was unable to rest. Paroxetine (20 mg/day) and clonazepam (0.5 mg/day) were administered through a gastrostoma, and the intensity and frequency of his attacks gradually decreased. Although his attacks ceased completely 14 days after surgery, his fear of additional attacks persisted, with no symptoms of agoraphobia; thus, the administration of paroxetine and clonazepam was continued. His physical condition recovered, and he was discharged with a tolerably mild degree of neck stiffness.

#### Comment

We have described two representative cases of first panic attack episodes in head and neck cancer patients that appeared to have been triggered by neck stiffness after radical surgery. In general, physical symptoms resulting from anxiety, such as palpitations or breathlessness, tend to be the main component of panic attack symptoms.

In the present cases, the features of their panic attack symptoms were distinct in that their most terrifying bodily sensation was neck stiffness, as if they were being strangled.

The onset of these panic attacks can be partially explained by the cognitive model of panic (Fig. 1).<sup>7</sup> Cervical discomfort, similar to tightening, probably increased the patients' apprehension—particularly under postoperative circumstances where the patients were forced to stay in bed with many drains and other lines inserted. Apprehension induces physical sensations associated with anxiety, such as palpitations and shortness of breath, feelings of

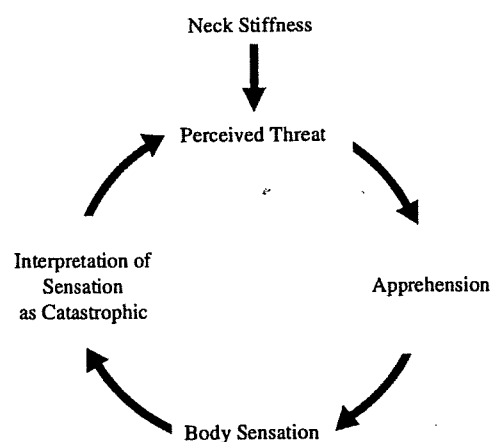


Fig. 1. The panic attack process, as illustrated by a cognitive model of panic.

choking, and so on. The patients interpreted both these apprehension-induced sensations and their neck stiffness as being catastrophic and were extremely fearful of death. Once this vicious cycle of symptoms had started, the patients were unable to cope by themselves. Their fear and physical sensations continued to grow, ultimately resulting in a panic attack.

Neck stiffness and pain sometimes appear after radical neck surgery and may be an aspect of the postradical neck pain syndrome.<sup>4-6</sup> Injury to the superficial cervical plexus is suspected to be one of the causes of this pain. Sist et al. reported the characteristics of 25 cases of post-radical neck pain syndrome. In their series, most of the patients reported that the intensity of their pain varied throughout the day, and many psychological or autonomic symptoms—including fear, punishment, and feelings of suffocation—emerged concomitant with the pain.<sup>6</sup> Although standardized psychiatric evaluations were not performed in this previous study, panic attacks or limited-symptom attacks might have occurred in some of the patients.

In the present cases, the panic attacks were alleviated after using a psychoeducational approach and commonly used psychopharmacological treatments. In general, delirium is first suspected when patients express restlessness after operations, but clinicians should be aware of the possible development of panic attacks after radical neck surgery. Patients undergoing radical head and neck surgery may be at risk for a panic attack; further research regarding this hypothesis is necessary.

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ORIGINAL ARTICLES

## Unexpectedly high prevalence of akathisia in cancer patients

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### ABSTRACT

**Objectives:** Complications of neuropsychiatric disorders are often detected in cancer patients. Adjustment disorders, depression, or delirium are common psychiatric disorders in these patients, and drug-induced neuropsychiatric problems are sometimes referred for psychiatric consultation. Prochlorperazine and other antiemetic drugs that are phenothiazine derivatives are also reported to cause akathisia due to the blockade of the dopamine receptor in the central nervous system, but the prevalence of akathisia in patients undergoing cancer treatment has not been reported. This study seeks to explore the prevalence of such drug-induced syndromes (e.g., akathisia) in this population.

**Methods:** This present study was a prospective study. The subjects of this study were 483 consecutive patients with cancer who had been referred to the Department of Psychiatry in Kanagawa Prefecture Cancer Center from February 1, 2004, to November 30, 2005. Trained psychiatrists conducted a nonstructured psychiatric interview and neurologic examination to establish psychiatric diagnoses according to DSM-IV and the presence or absence of drug-induced extra pyramidal symptoms. The past and current medications used in their cancer treatment were also examined in detail for an accurate evaluation.

**Results:** A psychiatric diagnosis was made in 420 (87.0%) of the 483 cancer patients examined, and akathisia, a drug-induced movement disorder, was unexpectedly prevalent among the patients; 20 of 420 (4.8%) patients had developed akathisia from an antiemetic drug, prochlorperazine.

**Significance of results:** Diagnosing such adverse drug reactions may be difficult due to complicating factors in cancer treatment, and the inner restlessness observed in akathisia is likely to be regarded as a symptom of a primary psychiatric disorder. The authors suggest that oncologists should optimize the use of antiemetic drugs and be aware of akathisia as a possible complication of cancer treatment.

**KEYWORDS:** Adverse drug reaction, Akathisia, Cancer, Prochlorperazine, Psychiatric referral

## INTRODUCTION

Neuropsychiatric disorders are often observed in cancer patients. In an initial study, Derogatis et al. (1983) reported that a psychiatric diagnosis was made in 47% of cancer patients, and adjustment disorders were the most frequent (68%), followed by depression (13%) and delirium (8%). A recent Japanese study of 1721 psychiatric referrals at a cancer center revealed that the most frequent psychiatric diagnoses, which were made according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV; American Psychiatric Association, 1994), were adjustment disorders, followed by delirium, major depression, dementia, and schizophrenia (Akechi et al., 2001). Among the psychiatric referrals, neuropsychiatric conditions associated with adverse drug reactions are sometimes detected. These conditions are sometimes difficult to diagnose because of multiple complicating factors in patients undergoing cancer treatment and oncologists' unfamiliarity of these conditions. Medication-induced movement disorders, a DSM-IV diagnostic category, are one of these conditions. This category includes neuroleptic-induced acute akathisia, neuroleptic malignant syndrome, and so on.

Akathisia is characterized by subjective feelings of restlessness accompanied by objective signs of motor restlessness such as fidgety movements of the legs and an inability to sit or stand still (American Psychiatric Association, 1994). Antiemetic drug-induced akathisia in cancer patients has been reported previously (Fleishman et al., 1994); a retrospective study confirmed that an antiemetic drug was one of the risk factors of akathisia in cancer patients (Gattera et al., 1994). But the incidence of akathisia among psychiatric referrals in a cancer center has not been published to date.

## SUBJECTS AND METHODS

This present study was a prospective study. The subjects of this study were 483 patients (225 males, 258 females; mean age  $\pm$  SD = 58.9  $\pm$  13.5 years) with cancer who had been referred to the Department of Psychiatry in Kanagawa Prefecture Cancer Center from February 1, 2004 to November 30, 2005. The consultation was requested for psychiatric evaluation, diagnosis, and treatment. The prevalence of the various sites of cancer was as follows: head and neck,  $n = 60$ , 12.4%; lung,  $n = 58$ , 12.0%; breast,  $n = 55$ , 11.4%; leukemia,  $n = 50$ , 10.4%; stomach,  $n = 35$ , 7.2%; uterus,  $n = 33$ , 6.8%; rectum,  $n = 21$ , 4.3%; esophagus,  $n = 20$ , 4.1%; colon,  $n = 19$ , 3.9%; pancreas,  $n = 18$ , 3.7%; and others,  $n = 114$ , 23.6%.

The psychiatric interviews were consecutively conducted with the patients by well-trained psychiatrists. The past and current medications used in their cancer treatment were also examined in detail for an accurate evaluation. The psychiatric diagnoses were made according to DSM-IV.

This study was not referred to the ethics committee of the cancer center and informed consent was not obtained from the patients because psychiatric interview, assessment, and diagnosis were within our routine work and extraordinary burdens and intervention were not placed on these patients.

## RESULTS

The prevalence of the various psychiatric diagnoses are listed in Table 1. A psychiatric diagnosis (axis I diagnosis of DSM-IV) was made in at least 420 of 483 cases (87.0%). Although the psychiatric diagnoses were diverse, the most frequent psychiatric diagnoses were adjustment disorders (30.2% of all subjects diagnosed) followed by depression (30.0%), and delirium (13.9%). Tied for fourth as most prevalent diagnoses were a medication-induced movement disorder (acute or tardive akathisia, 4.1%) and anxiety disorders (4.1%). Akathisia accounted for 4.8% of all psychiatric diagnoses. All patients with a movement disorder exhibited symptoms of akathisia, including a subjective feeling of restlessness and motor restlessness, such as an inability to sit and stand still. Half of these patients were diagnosed

**Table 1.** Psychiatric diagnoses (Axis I diagnosis of DSM-IV) in referred cancer patients

Psychiatric diagnosis	No. (N = 483)	Percent
Adjustment disorders	145	30.0
Mood disorders	124	25.7
Major depressive disorders	122	25.3
Bipolar disorder	2	0.4
Delirium	67	13.9
Medication-induced movement disorders	20	4.1
Anxiety disorders	20	4.1
Somatoform disorders	14	2.9
Schizophrenia and other psychotic disorders	11	2.3
Substance-related disorders	10	2.1
Dementia	9	1.9
Undetermined <sup>a</sup>	8	1.6
No diagnosis	55	11.4

<sup>a</sup>Eight patients were categorized as "undetermined" because of insufficient psychiatric interview time for a definitive diagnosis.

as having acute akathisia according to its onset after medication.

Table 2 shows the profiles of all the patients with akathisia (10 males and 10 females, mean age  $\pm$  SD:  $54.5 \pm 14.2$  years). Except for only two cases, akathisia had not been diagnosed until the psychiatric referral; these patients were referred to the psycho-oncologist because of their mental state, such as restlessness, anxiety, agitation, and so forth. Akathisia was induced by an antiemetic drug, prochlorperazine, in 16 of 20 patients; 3 were given 10 mg, and 13 were given 15 mg of prochlorperazine daily. In three cases, haloperidol, an antipsychotic agent, induced the akathisia. The onset of akathisia varied from 1 day to 9 months after the dopamine antagonist was prescribed.

## DISCUSSION

In this study, akathisia was the fourth most common psychiatric diagnosis among all the psychiatric referrals. In almost cases, the akathisia was induced by an antiemetic drug, prochlorperazine, which was

given for treating the nausea caused by morphine. Prochlorperazine is a phenothiazine derivative, and its antiemetic effect is due to its blockade of the central dopaminergic system; this dopaminergic blockade possibly causes extrapyramidal symptoms at the same time (O'Hara, 1958; Bateman et al., 1989). Prochlorperazine-induced akathisia in cancer patients has been reported previously. Fleishman et al. (1994) conducted a telephone interview of 24 cancer patients who had taken prochlorperazine and metoclopramide, another antiemetic drug, with chemotherapy and found that 50% of the patients had subjective motor restlessness. Gattera et al. (1994) determined risk factors of akathisia in terminally ill patients by a retrospective control study; exposure to haloperidol, prochlorperazine, promethazine, or morphine was a factor that predisposed patients to akathisia, respectively. Akathisia should be considered in patients to whom antiemetic drugs are administered, and in the present study, the authors prospectively examined the prevalence of neuropsychiatric complications in cancer patients and found an unexpectedly high prevalence of akathisia among

**Table 2.** Clinical characteristics of the 20 patients with akathisia

No.	Age	Sex	Cancer site	Reason for psychiatric referrals	Current prochlorperazine treatment	Current opioid treatment	Other dopamine blockers	Onset of akathisia after the start of medication (days)
1	51	M	neck	restlessness	15 mg	+		13
2	44	F	colon	bizarre behavior	15 mg	+		3
3	69	F	breast	anxiety	15 mg	+		1
4	82	F	uterus	loss of vigor	-	-	Haloperidol 1.5 mg	1
5	63	M	stomach	irritability, restlessness	15 mg	+		30
6	46	F	small intestine	restlessness	15 mg	+		33
7	39	M	lung	anxiety, insomnia	15 mg	+		58
8	57	F	breast	severe mental illness	15 mg	+		7
9	27	M	stomach	restlessness	10 mg	+		14
10	57	F	lung	depressive state	15 mg	+		30
11	46	F	bone	restlessness	15 mg	+		93
12	60	F	others	restlessness	15 mg	+		285
13	57	M	lung	restlessness	15 mg	+		97
14	66	M	esophagus	agitation	-	-	Haloperidol 5 mg	2
15	71	M	pancreas	restlessness	15 mg	+		17
16	72	M	stomach	anxiety	10 mg	+		31
17	50	M	colon	inability to sit	10 mg	+		36
18	40	M	myeloma	anxiety	-	+	Chlorpromazine 10 mg	3
19	58	F	lung	restlessness	15 mg	+		28
20	32	F	leukemia	agitation	-	+	Haloperidol 5 mg	12



patients. Prior to the referrals, only two oncologists had suspected akathisia. They referred the patients because of "unexpected behavioral changes," "bizarre behavior," and so on, and therefore asked for a psychiatric evaluation.

Whereas the first, second, and third most common psychiatric disorders observed in cancer patients referred for psychiatric evaluation were consistent with observations in previous studies, akathisia was more frequent in our study compared to previous ones (Massie & Holland, 1987; Grassi et al., 2000; Akechi et al., 2001). It is not clear why there are differences in the prevalence of various psychiatric diagnoses among the studies. Were most of the cases of akathisia overlooked or misdiagnosed in the previous studies? Although unlikely, the clinical impact of akathisia might have been underestimated. Another possibility is that akathisia was not categorized in the list of psychiatric diagnoses in the previous studies. Akathisia is not listed among the mental and behavioral disorders in the ICD-10 classification and DSM-III; DSM-IV newly adopted it as an axis I disorder. Another important factor is the misuse of prochlorperazine. Morphine was administered in 18 of 20 cases with akathisia in the present study. Nausea and vomiting is an initial adverse reaction in patients taking oral morphine. Prochlorperazine had been given to treat nausea induced by morphine, but its long-term administration was continued for no clear reason in almost all the cases.

Although psychotropic drugs are often used in palliative care, adverse drug reactions to psychotropics are sometimes overlooked. Two cancer patients who developed neuroleptic malignant syndrome, a potentially lethal adverse reaction of psychotropic drugs, have been reported previously. These patients developed neuroleptic malignant syndrome following bone marrow transplantation and in an intensive care unit on the day of surgery. The malignant syndrome was overlooked (Onose et al., 2002; Kawanishi et al., 2005). Diagnosing such adverse reactions is difficult due to multiple complicating factors associated with cancer treatment, its unfamiliarity to clinical oncologists, and occasionally the resemblance of these neuropsychiatric symptoms to those associated with cancer.

Akathisia is uncomfortable for patients; Atbaşğlu et al. (2001) found that the subjective awareness of akathisia is associated with suicidal ideation. Although akathisia is commonly observed in patients treated with neuroleptic drugs, it is sometimes overlooked or misdiagnosed (Weiden et al., 1987; Hirose, 2003). Akathisia often occurs without the coexistence of other extrapyramidal symptoms, and its characteristic symptoms, including inner restlessness,

tend to be regarded as representations of a symptom of a primary psychiatric illness. Therefore akathisia can be overlooked or misdiagnosed sometimes even in psychiatric units.

Based on these results, the use of antiemetic drugs should be optimized. In addition, clinical oncologists should be aware of akathisia. The management of adverse drug reactions is necessary during palliative care and contributes to patients' quality of life.

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## CASE REPORT

# Detection and treatment of akathisia in advanced cancer patients during adjuvant analgesic therapy with tricyclic antidepressants: Case reports and review of the literature

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## ABSTRACT

**Objective:** There is substantial evidence that tricyclic antidepressants are effective in the management of chronic pain, including cancer pain. In oncological settings, these agents are used as adjuvant analgesic drugs. However, cases of akathisia due to tricyclic antidepressants used as adjuvant analgesic therapy have not previously been reported.

**Case reports:** Two cancer patients experiencing chronic pain who were refractory to nonsteroidal anti-inflammatory drugs and opioids were prescribed amoxapine as an adjuvant analgesic therapy for neuropathic pain. These patients developed inner restlessness and restless physical movements after amoxapine was prescribed. Although symptoms were atypical, akathisia was suspected and discontinuation of amoxapine resolved the symptoms.

**Results and significance of results:** Akathisia should be considered in patients receiving adjuvant analgesic therapy with tricyclic antidepressants. Early detection and appropriate treatment will relieve this distressing symptom. Restless movements involving parts of the body other than the legs may be the clue to the diagnosis.

**KEYWORDS:** Cancer, Pain control, Akathisia, Tricyclic antidepressants

## INTRODUCTION

Akathisia is a common adverse effect of antipsychotics and, less commonly, antidepressants (Khawam et al., 2006). The clinical picture of akathisia involves subjective complaints of restlessness accompanied

by observable restless movements (e.g., fidgety movements of the legs, rocking from foot to foot, pacing, or the inability to sit or stand still) developing within a few weeks of starting or raising the dose of antipsychotics and/or antidepressants (American Psychiatric Association, 1994). The reported prevalence of akathisia has varied between 20% and 75%. Its onset is within a few days of initiation of medication, but it can also occur later in the treatment course (Hsin-Tung & Simpton, 2000).

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Akathisia can cause great discomfort and even agitation and is often described by the patient as the most distressing sensation, and suicide is a reported complication (Shear et al., 1983; Atbaşgılı et al., 2001). However, the condition is often underdiagnosed or misdiagnosed as anxiety, agitation, and violent behavior (Siris, 1985; Rodgers, 1992; Hirose, 2003). The reasons for underdiagnosis are considered related to both the patient's symptoms and the clinician's attitude toward akathisia. Patient-related factors include mild degree of akathisia, lack of apparent motor restlessness, lack of clear communication about subjective sensations of restlessness, restlessness in body areas other than the legs, and other clinical signs. Clinician-related factors include overemphasis on objective restlessness, failure to consider akathisia during antipsychotic therapy, and failure to fully implement antiakathisia treatments in ambiguous cases (Hirose, 2003).

There is substantial evidence that tricyclic antidepressants are effective in the management of chronic pain, including cancer pain (Botney & Fields, 1983; Hamon et al., 1987; Magni et al., 1987). In oncological settings, these agents are used as adjuvant analgesic drugs and are administered along with a primary analgesic, usually an opioid, to treat pain that is refractory to analgesic treatment alone (Portenoy, 2001). However, cases of akathisia due to tricyclic antidepressants used as adjuvant analgesic therapy have not previously been reported.

In this communication, we report two advanced cancer patients who developed akathisia due to adjuvant analgesic therapy with tricyclic antidepressants.

To standardize physicians' judgements, Francis' criteria (Francis et al., 1990) were proposed to diagnose akathisia. These criteria are based of a combination of clinical assessment and medical chart review, and the potential cause was categorized as (1) definite, if it was temporally related, there was laboratory confirmation, the patient improved with treatment or cessation of the offending agent, and there was no other cause present or (2) probable, if all the previous criteria were met but another main cause was present or laboratory confirmation was not achieved. In this study, we used the probable criteria because akathisia was confirmed only by clinical observation and careful inquiry, not by laboratory data.

## CASE REPORTS

### Case 1

A 39-year-old female had been diagnosed as having breast cancer 8 years previously and had received a

mastectomy followed by chemotherapy and hormonal therapy. Metastasis of cancer was recognized in the liver and bone and chemotherapy was performed. She developed lumbago that was refractory to non-steroidal anti-inflammatory drugs and opioids and was thought to be neuropathic in origin. She was administered 75 mg/day of amoxapine, an tricyclic antidepressant, as an adjuvant analgesic therapy. Five months after administration of amoxapine, she suddenly became restless and moved her arms and upper part of the body back and forth. She reported a sensation of inner restlessness in both upper arms, abdomen, and back, but denied such inner restlessness in the lower extremities or legs. Based on this clinical picture, akathisia was suspected, although clinical findings were atypical in that restlessness in the legs was not observed. Amoxapine was discontinued and the inner restlessness was resolved the next day.

The clinical findings and effective alleviation of symptoms after discontinuation of medication fulfilled Francis' criteria for drug-induced akathisia.

### Medical history

The patient was a housewife, and had no medical history of psychiatric illness or alcohol or drug abuse. She had a normally cooperative character and was kind to others.

### Case 2

A 54-year-old rectal cancer patient developed pain of the left lower thigh. He was treated with 180 mg of loxoprofen sodium, 1.8 mg of fentanyl, and 10 mg of prochlorperazine for about 1 month. As the pain was refractory to conventional therapy and thought to be neuropathic in origin, he was prescribed 10 mg of amoxapine as an adjuvant analgesic therapy. Ten days after administration of amoxapine, he sometimes woke up and walked around the ward slowly, but could not continue because of poor physical condition. He sometimes chewed gum and sucked candies. After careful inquiry, he reported a subjective sensation of inner restlessness in the lower extremities. As akathisia was suspected, prochlorperazine was discontinued first because of the dopamine receptor blockade property of prochlorperazine; however, symptoms of akathisia did not change during the following 2 days. Then amoxapine was discontinued and both motor and inner restlessness were resolved in 2 days. He also stopped chewing gum and sucking candies. The patient explained that he had felt restlessness in the mouth and chewed gum and sucked candies to relieve this sense of inner restlessness.

The clinical findings and effective alleviation of symptoms after discontinuation of medication fulfilled Francis' criteria for drug-induced akathisia.

#### Medical history

The patient had no medical history of psychiatric illness or alcohol or drug abuse. He had normally cooperative character and was kind to others.

### DISCUSSION

Tricyclic antidepressants can be used as adjuvant analgesic drugs. Experimental studies indicate that these drugs potentiate the action of morphine by blocking serotonin reuptake and enhancing the action of serotonin at the spinal terminals of the opioid-mediated intrinsic analgesia system (Botney & Fields, 1983; Hamon et al., 1987).

These drugs also have extrapyramidal side effects, and amoxapine has been shown to have neuroleptic properties along with antidepressant effects (Krishnan et al., 1984; Apiquian et al., 2005). It appears that the 7-hydroxy metabolite of amoxapine causes a dopamine receptor blockade (Dolton, 1981).

We reported two cases of akathisia due to tricyclic antidepressants administered for adjuvant analgesic therapy. This is the first report of akathisia induced by adjuvant analgesic therapy using tricyclic antidepressants. Our report suggests that akathisia should be considered a possible side effect during adjuvant analgesic therapy.

In diagnosing akathisia, the typical clinical picture includes inner restlessness and fidgety and restless movement of the body, particularly in the legs. DSM-IV criteria describe restless movements expressed mainly in the legs, and these movements are considered highly characteristic to akathisia (American Psychiatric Association, 1994). However, it has been reported that restless movements may occur in other areas of the body such as arms or abdomen (Ratey & Salzman, 1984; Walters et al., 1989) and may present as dyspnea (Hirose, 2000). It has been reported that leg restlessness is recognized in only 27% (Gibb & Lees, 1986) and 55% (Sachdev & Kruk, 1994) of the cases.

Case 1 did not report inner restlessness or show restless movements involving the lower extremities or legs. In case 2, restlessness in the mouth has been reported and the patient relieved this sensation in the mouth by chewing gum. And it was difficult to recognize restless movements because the physical condition of the patient was poor and he lay down on the bed almost all day. Although the clinical pictures of akathisia in these patients included atypical

features, discontinuation of the suspected drug effectively alleviated symptoms.

Our study suggests that it is important to detect signs and symptoms of akathisia from these subtle combinations of movements. Slow but repeated movements and atypical movements involving areas other than legs together with reports of inner restlessness might be clues to diagnose these patients. The temporal relationships between administration of the drug and the development of symptoms are also important.

Physicians, nurses, pharmacists, and other health professionals should be aware of this possible side effect during adjuvant analgesic therapy. Early detection and appropriate management will improve the quality of life for these patients.

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