Table 3. Association between patients' unmet needs (SCNS-SF34) and psychological distress (HADS)/quality of life (EORTC QLQ-C30 Global health status)

	Spearman's correlation coefficient				
	SCNS-SF34				
	Physical and daily living domain	Psychological domain	Sexuality domain	Patient care support domain	Health system and information domain
HADS total	0.59 (0.43–0.71)*	0.69 (0.56–0.79)*	0.19	0.51 (0.33–0.65)*	0.52 (0.34–0.66)*
EORTC QLQ-C30 Global health status	−0.69 (−0.55 to −0.79)*	−0.45 (−0.26 to −0.61)*	0.12	−0.44 (−0.60 to −0.25)*	−0.41 (−0.57 to −0.22)*

EORTC QLQ-C 30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.
*$P < 0.01$.

assessment of unmet or special needs may not be useful for improving the psychological distress of patients with advanced breast cancer. Case management based on several unmet needs, including physical unmet needs, is needed.

This study has several limitations. First, as our study used a cross-sectional design, we cannot be sure of the cause–effect relationship. Distress may create unmet needs, or unmet needs may generate distress; alternatively, a third factor may give rise to both unmet needs and distress. Second, the observed correlations among needs, distress and QOL may not be causal at all but simply represent conceptual overlaps among the respective measures. Third, because we invited outpatients to participate in the present study, most of the patients did not have any physical functioning impairments. Thus, our results do not reflect the unmet needs of advanced cancer patients with severe physical impairment. Finally, the sample size was not sufficiently large to use more rigorous statistical analyses such as multiple regression analysis, limiting the generalizability of these results to all advanced breast cancer patients.

Despite these limitations, this study has some important strengths. We used well-validated and reliable tools to assess psychological status and QOL, which should help to obtain generalizable results. We also selected the patients who have the same cancer type (breast cancer), similar physical status and advanced cancer to match QOL and needs, so we concentrated on a homogenous sample of patients. In addition, only a few patients refused to complete the questionnaires.

The present study revealed close associations among the various domains of unmet needs, psychological distress and QOL among patients with advanced breast cancer but without grave physical impairments. Clinicians must pay greater attention to unmet needs and provide appropriate services and resources. However, we do not know what kind of services and resources are suitable for these unmet needs now. Given the multitude of unmet needs among these patients, multifaceted interventions targeting various domains of unmet needs should be developed and tested to decrease the psychological distress of these patients.

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Conflict of interest statement

Toshiaki Furukawa daclares that he has received honoraria for speaking at CME meetings sponsored by Astellas, Dai-Nippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Kyorin, MDS, Meiji, Otsuka, Pfizer, Shionogi and Yoshitomi. He is on the advisory board for Sekisui Chemicals and Takeda Science Foundation. He has received royalties from Igaku-Shoin, Seiwa-Shoten, Nihon Bunka Kagaku-sha and American Psychiatric Publication. The Japanese Ministry of Education, Science, and Technology and the Japanese Ministry of Health, Labor, and Welfare have funded his research.

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quetiapine, aripiprazole, blonanserin), antidepressants (fluvoxamine, sertraline, paroxetine, milnacipran, mirtazapine) and thyroxine, her mood fluctuated frequently, including nine depressive phases and five hypomanic phases in the 26 months after the first admission, with euthymic periods lasting less than 3 weeks. Several drugs could not be used to sufficient doses due to side-effects; however, most drugs were used to adequate doses and durations. Consequently, she was admitted eight times (total duration: 332 days) due to depressive episodes. On her third and fifth admissions, six bilateral ECT sessions were performed consecutively for acute-phase severe depressive symptoms and moderate improvement was observed. During these two ECT sessions, medications were not changed. In consideration of the outcome of the two previous acute-phase ECT sessions, ambulatory continuation-ECT was started 26 months after the first admission. Continuation-ECT was administered weekly for the first month and subsequently reduced to biweekly administration. In the subsequent 12 months of C/M-ECT, she did not reach remission; however, her HRSD score decreased to 14 and her YMRS score decreased to 7, indicating reduced severity of depression and decreased hypomanic state. To date, she has not been hospitalized.

Antidepressants, particularly tricyclic antidepressants, are reportedly responsible for inducing 20% of RC cases;[1] however, in our patient, most hypomanic phases occurred when she was antidepressant-free. Regarding the C/M-ECT schedule, we could not extend beyond 2-week treatment intervals, which is similar to a report indicating that maintenance-ECT could not be extended beyond 3-week treatment intervals for patients with BD.[2] Although she did not achieve complete remission, our experience suggests that C/M-ECT could reduce the likelihood of re-admission by decreasing the severity of RC, thereby providing a cost-effective treatment. Except for one naturalistic study of 14 RC patients,[3] research on the effectiveness of C/M-ECT is limited. In order to evaluate the efficacy of C/M-ECT and establish a standard protocol for BD, further study in a large sample or in a controlled study is needed.

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Kaichiro Amino, MD[1,2] Shigemasa Katayama, MD, PhD[1,2] and Makio Iimori, MD, PhD[2]

[1]*Department of Psychiatry, Seijin Hospital* and [2]*Department of Psychiatry, Tokyo Medical University Graduate School of Medicine, Tokyo, Japan*

Email: kamino@seijin.org

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Case of intrathecal baclofen-induced psychotic symptoms

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BACLOFEN, AN ANTAGONIST of inhibitory neurotransmitter gamma-aminobutyric acid (GABA) receptors, is currently the most widely used drug for the treatment of spasticity. Intrathecal baclofen (ITB) is approved for the treatment of spasticity of spinal or cerebral origin in patients who are intolerant of, or unresponsive to, oral baclofen. To the best of our knowledge, the extant literature reporting psychiatric symptoms co-occurring with ITB therapy in adults is limited.[1] We report herein a case of psychotic manifestations induced by ITB administration. We have obtained the oral consent of this patient to report her case.

Mrs A was a woman in her 50s who had neither a family history nor a personal history of psychiatric illness. In the year 200X-5, she received a head injury in a traffic accident and was diagnosed as having diffuse axonal injury. She subsequently suffered from limb dystonia, and ITB therapy was started in December 200X-1. Her physician temporarily increased the baclofen dose to 1400 μg/day, which is regarded as the maximum dosage (the normal therapeutic dose is up to 250 μg/day), due to pain and rigidity of limbs. Negativism, delusions concerning her own name ('My name is B, not A!') and her husband ('I have already divorced him, and I have another husband'), persecutory delusions of being observed and poisoned, delusions of interpretation, and acousma appeared a few days after the baclofen dosage was increased to the maximum value. Therefore, the physician decreased the baclofen dosage to 250 μg/day. However, the patient's hallucinations and delusions did not improve. She had difficulty with daily living because of her psychotic symptoms, and she had to be admitted involuntarily to the inpatient ward of psychiatry in April 200X. Olanzapine (maximum dosage of 20 mg/day) and risperidone (maximum dosage of 8 mg/day) were both administered, but neither of these treatments was effective. Finally, her psychotic symptoms improved dramatically when we reduced the baclofen dosage to 50 μg/day in May 200X. The patient's blood laboratory data and a cranial computed tomography scan were within the normal limits; the patient refused to undergo an electroencephalogram. The patient remembered the episode after her symptoms had disappeared, commenting, 'I felt that I was in a long dream.' In December 200X, she requested to re-increase her baclofen dosage because of stiffening and pain in her limbs. Psychotic symptoms similar to her previous episode re-appeared when the baclofen dosage was re-increased to 80 μg/day, which then subsided only after the dosage was decreased to 50 μg/day.

We clinically determined that her diagnosis was not delirium for the following reasons. At first, her symptoms did not completely meet with the DSM-IV diagnostic criteria. For example, her condition was not fluctuating and there was no circadian variation. In addition, neither the sleep–wake rhythm disturbance nor decrease of alertness was observed. Recurrence of the psychiatric episode after re-increase of the baclofen dosage supports the view that ITB intoxication

induced psychiatric symptoms. Finally, it should be noted that baclofen withdrawal as well as intoxication can induce psychiatric symptoms.[2]

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Ryuichi Sagawa, MD, PhD,[1] Aiko Yoshida, MD,[1] Tadashi Funayama, MD,[1] Toru Okuyama, MD, PhD,[1] Tatsuo Akechi, MD, PhD[1] and Toshiaki A. Furukawa, MD, PhD[2]
[1]*Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi,* and [2]*Department of Health Promotion and Human Behavior (Cognitive-Behavioral Medicine), Kyoto University Graduate School of Medicine/School of Public Health, Sakyo-ku, Kyoto, Japan*
Email: rsagawa@med.nagoya-cu.ac.jp
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Chronic Cotard's syndrome: Recovery from 2 years' bed-ridden status

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COTARD'S SYNDROME WAS first described by Dr Jules Cotard in 1880.[1] Typically, patients believe that they have lost organs, body parts, or even that they have died. However, recent reports have described little about successful drug treatments.[2,3] Here we report a woman suffering from Cotard's syndrome for more than 2 years who did not receive any psychiatric therapeutics, but showed dramatic improvement when treated with fluoxetine and risperidone at a later time.

'Ms C', a 59-year-old female patient, had been through multiple life stresses for the past 5 years. Initially, she presented general weakness, which led her to several hospital visits. Gradually, poor sleep, poor appetite, and loss of energy developed. She also complained constantly that both her legs were paralyzed. Finally, she could no longer walk and then was placed in a nursing home by her family and had been living there for more than 2 years.

She was brought to our hospital for generalized pain. Initial surveys, including physical examinations, serum chemistry, and hematology profile, were all within normal limits. She was admitted to our acute ward for further evaluations.

On admission, depressive symptoms, including loss of energy and feelings of hopelessness, were noted. She also expressed bodily delusions, delusions of negations, and delusions of being paralyzed. Further investigations, including electromyography, nerve conduction velocity testing and brain magnetic resonance imaging, all showed negative findings.

On exclusion of organic causes, Cotard's syndrome, in the context of major depressive disorder with psychotic features, was diagnosed. Fluoxetine 40 mg/day with risperidone 6 mg/day was prescribed to treat the depressive and psychotic symptoms. During the first month, the patient was bed-ridden and needed special nursing care. Gradually, her depressive symptoms and delusions subsided. After 2 months, she started to walk again and then was discharged in a stable condition.

Similar to Yamada's report,[1] our patient's clinical course can be divided into the germination stage (cenesthopathy and hypochondriasis), the blooming stage (full development of symptoms of Cotard's syndrome) and the chronic stage (systematization of delusions). Although electroconvulsive therapy is suggested in the chronic stage,[1] our patient's condition improved dramatically with combination therapy of fluoxetine and risperidone. To our knowledge, this is the first report about successful pharmacological treatments in the chronic stage of Cotard's syndrome in the medical literature. It is probably related to risperidone's stabilizing effects on the hyperactivity of dopamine systems in Cotard's syndrome[4] and enhancement of antidepressant effects of fluoxetine via alpha-2 adrenergic receptors,[5] but the exact mechanism requires further study.

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Po-Han Chou, MD, Ben-Tang Lin, MD, Tsuo-Hung Lan, MD and Chin-Hong Chan, MD
Department of Psychiatry, Taichung Veterans General Hospital, Taichung, Taiwan
Email: lonelymanym@yahoo.com.tw
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Psychotic-like experiences are associated with violent behavior in adolescents

Yoshihiro Kinoshita [a,1], Shinji Shimodera [b,1], Atsushi Nishida [c,*], Kuni Kinoshita [a], Norio Watanabe [a], Norihito Oshima [d], Tatsuo Akechi [a], Tsukasa Sasaki [e], Shimpei Inoue [b], Toshi A. Furukawa [a], Yuji Okazaki [f]

[a] Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
[b] Department of Neuropsychiatry, Kochi Medical School, Kochi, Japan
[c] Department of Schizophrenia Research, Tokyo Institute of Psychiatry, 2-1-8 Kamikitazawa, Setagaya-ku, Tokyo 156-8585, Japan
[d] Office for Mental Health Support, Division for Counseling and Support, The University of Tokyo, Tokyo, Japan
[e] Division of Developmental Sciences, Graduate School of Education, The University of Tokyo, Japan
[f] Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital, Tokyo, Japan

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ABSTRACT

Objective: The diagnosis of psychotic disorder is associated with a risk of violence. Psychotic-like experiences (PLEs) in the general population may share an etiological background with psychotic disorders. The present study has evaluated the association between PLEs and violent behavior in adolescents.
Methods: PLEs and violent behavior were assessed using a self-report questionnaire administered to 18,104 Japanese adolescents. Potential confounding factors were also evaluated.
Results: After controlling for the effects of age, gender, GHQ-12 total score, victimization, and substance use, the existence of PLEs was significantly associated with both interpersonal violence (odds ratio (OR) = 1.36, 95% confidence interval (CI): 1.23 to 1.51) and violence towards objects (OR = 1.46, 95%CI: 1.33 to 1.61). The greater the number of such psychotic experiences, the higher the risk of violence. Particular types of PLEs ('spied-upon' and 'voice hearing') are significantly associated with interpersonal violence, while all of the types of PLEs assessed in this study were significantly associated with violence towards objects.
Conclusion: PLEs may be a risk factor for violent behavior in adolescents. Violent acts by individuals with schizophrenia may not be a direct consequence of the disease itself, but may instead share an etiological background with such behavior in the general population.

1. Introduction

Recent studies suggest that positive psychotic symptoms exist on a continuum, with psychotic disorder at one end and non-clinical psychotic-like experiences (PLEs) at the other (Stip and Letourneau, 2009; van Os et al., 2000; Verdoux and van Os, 2002). Indeed, PLEs are a common phenomenon in the general population, including adolescents. For instance, in a large sample of more than 7000 men and women aged between 18 and 64 taken from the general population, van Os et al. (2000) revealed that 17.5% of the participants had reported at least one experience evoking the concept of psychosis. Furthermore, some studies have suggested that PLEs in childhood and adolescence may be risk factors for later psychiatric disorders and harmful behavior, including violence (Chapman et al., 1994; Nishida et al., 2010; Poulton et al., 2000; Mojtabai, 2006).

Violence is one of the most problematic behaviors in adolescence, and is also associated with the diagnosis of a

* Corresponding author. Tel.: +81 3 33045701; fax: +81 3 33298035.
E-mail address: nishidaa@prit.go.jp (A. Nishida).
[1] Contributed equally to this work.

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psychotic disorder including schizophrenia (Junginger, 1996; Swanson et al., 2006; Walsh et al., 2002; Douglas et al., 2009). However, little is known about the potential mechanisms for the association between psychosis and violence (Foley et al., 2005, 2007). It is possible that violent behavior in individuals with schizophrenia can be explained by the continuum hypothesis (Stip and Letourneau, 2009; van Os et al., 2000; Verdoux and van Os, 2002), in which violence is also associated with non-clinical psychotic-like experiences. It may also be the case that such behavior in individuals diagnosed with psychotic disorders shares an etiological background with those in the general population. It is, therefore, valuable to examine if PLEs are associated with violent behavior in a non-clinical population. It is particularly important to confirm this potential association in adolescents, since this time of life is the peak period for violence (Reiss and Roth, 1993), and the onset of schizophrenia typically occurs after the late teens (Verdoux et al., 1998).

Although some research has revealed that PLEs were associated with violent behavior in the general population (Mojtabai, 2006), to our knowledge, few studies have reported an association between PLEs and violence among adolescents. Moreover, earlier research into the link between PLEs and violent behavior did not distinguish between interpersonal violence and violence towards objects, and nor did it examine if there is any difference between early and late adolescence.

The present study, therefore, aims to examine the contribution of PLEs to the occurrence of violent behavior in adolescents. The two hypotheses we would like to examine are:

1) Whether interpersonal violence and violence towards objects are directly associated with PLEs in adolescents.
2) Whether specific types of PLEs are associated with interpersonal violence and violence towards objects in adolescents.

2. Methods

2.1. Sample and survey procedures

In order to investigate the psychopathology in adolescence and examine its associated factors such as demographics, victimization and help seeking attitudes, we conducted a large community survey in Japan. This report focused on violence and its associated factors in adolescence. Between 2008 and 2009, we recruited students (aged between 12 and 18 years) from 45 public junior high schools (7th–9th grades) and 28 high schools (10th–12th grades) in Tsu City and Kochi Prefecture, Japan. We then conducted a cross-sectional survey of psychopathologies in this sample. The total populations of Tsu City and Kochi Prefecture are approximately 280,000 and 790,000 respectively. Attendance at junior high school is compulsory under the Japanese law, but attendance at high school is not.

After the study was approved by the ethics committees of the Tokyo Institute of Psychiatry, the Mie University School of Medicine and the Kochi Medical School, the principal investigators approached the schools' head teachers about participation in the research. These heads then consulted with teachers and parents.

The teachers at the participating schools were told about the guidelines for the distribution and collection of our questionnaires. They then gave these documents to the students, along with envelopes in which to place them after completion of the task. The teachers also explained: 1) that participation in the study was anonymous and voluntary, and 2) that strict confidentiality would be maintained. In addition, the students were asked to seal the completed questionnaire in the envelope they had been provided with. Each teacher also reported on the total number of present and absent students on the day the survey was administered (including those who had not been in attendance for more than a month). The research team later collected the sealed questionnaires from each school.

2.2. Measures

The questionnaires included items concerning the following: 1) psychopathological and behavioral problems, including PLEs, interpersonal violence and violence towards objects; 2) the Japanese version of the 12-item General Health Questionnaire (GHQ-12); and 3) other variables, including demographic characteristics.

2.2.1. Psychotic-like experiences

Psychotic-like experiences were assessed using five items adopted from the schizophrenia section of the Diagnostic Interview Schedule for Children (DISC-C) (Costello et al., 1985). These items have previously been used in a birth cohort study and are regarded as good predictors of schizophreniform disorder in adulthood (Poulton et al., 2000). The items were as follows: 1) "Some people believe in mind reading or being psychic. Have other people ever read your mind?"; 2) "Have you ever had messages sent just to you through the television or radio?"; 3) "Have you ever thought that people are following you or spying on you?"; 4) "Have you ever heard voices other people cannot hear?"; and 5) "Has something ever gotten inside your body or has your body changed in some strange way?". The participants were told that they should base their answers on whether they had ever experienced these symptoms at any point in their life. Possible responses included: 'no', 'yes, likely', and 'yes, definitely (only once or more than once)'. We defined 'yes, definitely' as the presence of a hallucinatory and delusional experience, and 'no' or 'yes, likely' as no experience. The number of experiences reported by an individual was designated as the 'total PLE score', with a range of 0–5. In addition, the number of delusional experiences reported by an individual was denominated as the 'delusional score of PLE', with a range of 0–4.

2.2.2. Interpersonal violence and violence towards objects

Questions about interpersonal violence and violence towards objects in the previous year were also included in the questionnaire. These two items were: "Have you physically abused someone in your family or your friends?" (for interpersonal violence within the past year) and "Have you been extremely frustrated and damaged something?" (for violence towards objects within the past year). There were two possible responses to these questions: 'yes' or 'no'. There is evidence that self-reports of violence correspond

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reasonably well with administrative records (Crisanti et al., 2005). Suicide was not included in the violent behavior in the present study.

2.2.3. The GHQ-12

The GHQ-12 is one of the most widely used self-report screening tools for non-psychotic psychiatric symptoms, particularly those of anxiety and/or depression (Goldberg et al., 1976). The validity and reliability of the Japanese version of the test have been confirmed (Doi and Minowa, 2003; Fukunishi, 1990). The GHQ was originally applied to adult populations, but was then used and validated for younger groups (Arakida et al., 2003; Kaneita et al., 2007; Radovanovic and Eric, 1983; D'Arcy and Siddique, 1984). A 4-point scale, with binary scoring (0011), which is known as the GHQ method, was used for each of the questions. Responses of '1' were then added together to form the total score, with a range between 0 (best possible) and 12 (worst possible). Individuals with a total GHQ-12 score ≥ 4 were considered to have poor mental health (Arakida et al., 2003; Fuchino et al., 2003; Kaneita et al., 2007). The total GHQ score was demonstrated to be associated with both PLEs (Nishida et al., 2008) and violence (Blitstein et al., 2005), and could be a potential confounding factor influencing the link between PLEs and violence.

2.2.4. Other variables

Violent behavior among a young population might be influenced by other confounding factors, such as victimization and substance use, as indicated in previous studies (Campbell and Morrison, 2007; Lataster et al., 2006; Hovens et al., 1994; Swanson et al., 1990; Spidel et al., 2010). In our questionnaire, we asked the participants about their experiences of being bullied (within the past year), violence from adults at home (within the past month), alcohol use (within the past month), and the use of recreational drugs (lifetime). The items concerning victimization ('being bullied' and 'violence from adults in the home'), alcohol use, and the use of recreational drugs were answered with a 'yes' or a 'no'.

2.3. Statistical analysis

Associations between PLEs and violent behavior in the previous year were analyzed using a logistic regression analysis, adjusted for age, sex, GHQ-12 total score, victimization ('being bullied' and 'violence from adults in the home') and substance use (alcohol use and the use of recreational drugs). In addition, the effect of the total PLE score was also tested. Interpersonal violence and violence towards objects were the dependent variables.

Associations between each of the five PLEs and the two types of violent behavior were examined by comparing individuals who had experienced each type of PLE to those who had not. A logistic regression analysis was again used to control for possible confounding factors. Additionally, in order to evaluate the effects of a combination of delusional and hallucinatory experiences on violence, we conducted another logistic regression analysis, adjusted for the potential confounding factors. ORs for the delusional score of PLE, voice hearing, and the interaction term for both of these factors were calculated through the analysis.

All of the statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). A two-tailed P-value<0.05 was considered to be statistically significant.

3. Results

3.1. Descriptive statistics

13 of 20 public junior high schools in Tsu City, and 32 of the 118 public junior high schools and 28 of the 36 public high schools in Kochi Prefecture, agreed to participate in the survey. Of all of the students in the relevant classes invited to take part ($n=19,436$), 18,638 were approached at school (798 were absent), of whom 18,250 agreed to contribute to the research. Of these 18,250 subjects, 18,104 (93.1% of all students in the relevant classes) gave analyzable responses. Of these 18,104 participants, 8992 were male (49.7%) and 9112 were female (50.3%). Their ages ranged from 12 to 18, with the mean age being 15.2 ($SD=1.7$). The mean and median of the total GHQ score were 3.53 ($SD=3.15$) and 3.00, respectively.

3.2. Prevalence of PLEs and violent behavior

The prevalence of the five PLEs was as follows: 'thoughts read' was observed in 343 individuals (1.9%), 'special messages' in 133 (0.7%), 'spied-upon' in 1157 (6.4%), 'voice hearing' in 1743 (9.6%), and 'somatic ideation' in 338 (1.9%). In addition, 2611 (14.4%) reported at least one type of PLE. In the previous 12 months, the two types of violent behavior with which we were concerned were reported by 4301 (23.8%) (interpersonal violence) and 6353 students (35.1%) (violence towards objects), respectively.

3.3. Associations between PLEs and violent behavior

The occurrence of at least one type of PLE was associated with an increased prevalence of both interpersonal violence and violence towards objects, even after controlling for age, sex, non-psychotic psychiatric symptoms (the GHQ-12 total score), victimization, and substance use (Table 1). There was no difference between high school (late adolescents, aged 15–18) and junior high school students (early adolescents, aged 12–15) in terms of trends in association between PLEs and violent behavior. Furthermore, the OR (adjusted for sex, age, drug and alcohol usage, violence from adults, being bullied, and GHQ-12 total score) for a one point increase in the total PLE score was 1.15 (95%CI: 1.08 to 1.22; $p<0.001$) for interpersonal violence and 1.28 (95%CI: 1.20 to 1.36; $p<0.001$) for violence towards objects. This indicates that these behaviors were more prevalent in individuals who had experienced a greater number of PLEs. Table 2 sets out the associations between the potential confounding factors and violence. All the factors except for alcohol use were independently associated with both interpersonal violence and violence towards objects. The relationship between alcohol use and interpersonal violence was statistically significant, though the association of alcohol intake to violence towards objects was not.

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Table 1
Associations between violent behaviors in the previous year and the lifetime occurrence of at least one type of PLE.

	Whole sample[a]				Junior high school				High school			
	Unadjusted OR (95%CI)	P	Adjusted OR[b] (95%CI)	P	Unadjusted OR (95%CI)	P	Adjusted OR[b] (95%CI)	P	Unadjusted OR (95%CI)	P	Adjusted OR[b] (95%CI)	P
Interpersonal violence	1.97 (1.81, 2.16)	<0.001	1.36 (1.23, 1.51)	<0.001	1.84 (1.63, 2.07)	<0.001	1.31 (1.14, 1.50)	<0.001	2.05 (1.78, 2.36)	<0.001	1.43 (1.22, 1.67)	<0.001
Violence towards objects	2.32 (2.13, 2.53)	<0.001	1.46 (1.33, 1.61)	<0.001	1.99 (1.80, 2.20)	<0.001	1.43 (1.25, 1.63)	<0.001	2.18 (1.93, 2.46)	<0.001	1.49 (1.30, 1.70)	<0.001
Interpersonal violence and/or violence towards objects	2.36 (2.16, 2.57)	<0.001	1.50 (1.36, 1.65)	<0.001	2.40	<0.001	1.46	<0.001	2.24	<0.001	1.53	<0.001

[a] In each section, the sample size ranged between 17,192 and 17,631 due to the missing data that have been excluded from the statistical analyses.
[b] Odds ratio adjusted for sex, age, drug and alcohol usage, violence from adults, being bullied, and GHQ total score.

3.4. Associations between specific PLEs and violent behavior

The effect of each of the five PLEs was analyzed by a logistic regression analysis. After controlling for age, sex, non-psychotic psychiatric symptoms (the GHQ-12 total score), victimization, and substance use, 'being spied-upon' and 'voice hearing' were significantly associated with interpersonal violence, while 'thoughts read', 'special messages' and 'somatic ideation' were not. All of the assessed PLEs ('thoughts read', 'special messages', 'spied-upon', 'hearing voices', and 'somatic ideation') were significantly related to violence towards objects (Table 3).

3.5. Effects of a combination of delusional and hallucinatory experiences on violence

Table 4 portrays the ORs (adjusted for sex, age, drug and alcohol usage, violence from adults, being bullied, and GHQ total score) for the delusional score of PLE, voice hearing, and the interaction term for both of these factors for violence. The ORs for the interaction term for the delusional score of PLE and voice hearing were 0.72 (95%CI: 0.60 to 0.86) for interpersonal violence and 0.77 (95%CI: 0.64 to 0.93) for violence towards objects.

4. Discussion

The present study has confirmed that PLEs are associated with the occurrence of interpersonal violence and violence towards objects in a large, locally-representative sample of adolescents (n = 18,104). A dose–response association was highlighted between the number of PLEs and the violent behavior; the greater the number of psychotic-like experiences, the higher the risk of the violence. No difference was found between high school (late adolescents, aged 15–18) and junior high school students (early adolescents, aged 12–15) in terms of trends in association between PLEs and violent behavior. With regard to the relationship between other important factors and violent behavior, this research replicated the previous one which demonstrated the significant associations of sex, age, poor mental health, victimization and substance use to violent behavior (Swanson et al., 1990;

Table 2
Associations between violent behaviors in the previous year and the potential confounding factors.

	Interpersonal violence		Violence towards objects		Interpersonal violence and/or violence towards objects	
	Adjusted OR[a] (95%CI)	P	Adjusted OR[a] (95%CI)	P	Adjusted OR[a] (95%CI)	P
Sex[b]	0.50 (0.46, 0.54)	<0.001	0.70 (0.65, 0.75)	<0.001	0.60 (0.56, 0.64)	<0.001
Age[c]	0.77 (0.75, 0.79)	<0.001	0.92 (0.90, 0.94)	<0.001	0.84 (0.83, 0.86)	<0.001
GHQ total score[d]	1.11 (1.10, 1.13)	<0.001	1.21 (1.19, 1.22)	<0.001	1.20 (1.19, 1.22)	<0.001
Being bullied	1.45 (1.27, 1.65)	<0.001	1.15 (1.01, 1.30)	<0.05	1.31 (1.15, 1.49)	<0.001
Violence from adults in the home	3.21 (2.69, 3.82)	<0.001	2.11 (1.77, 2.52)	<0.001	2.63 (2.16, 3.21)	<0.001
Alcohol use	1.70 (1.54, 1.89)	<0.001	1.96 (1.78, 2.15)	<0.001	1.99 (1.81, 2.19)	<0.001
Use of recreational drugs	1.26 (1.05, 1.52)	<0.05	1.15 (0.95, 1.39)	<0.14	1.20 (0.98, 1.47)	<0.08

In each section, the sample size ranged between 17,192 and 17,631 due to the missing data that have been excluded from the statistical analyses.
[a] Odds ratio calculated through the regression analyses conducted to obtain the adjusted ORs presented in Table 1.
[b] Male was used as referent.
[c] ORs were calculated for a one year increase in age.
[d] ORs were calculated for a one point increase in the GHQ total score.

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Table 3
Associations between violent behaviors and specific PLE.

	Interpersonal violence		Violence towards objects	
	Unadjusted OR (95%CI)	Adjusted OR[a] (95%CI)	Unadjusted OR (95%CI)	Adjusted OR[a] (95%CI)
Thoughts read	1.56 (1.24, 1.96)	0.99 (0.76, 1.28)	2.37 (1.91, 2.94)	1.64 (1.29, 2.10)[b]
Special messages	2.45 (1.73, 3.46)	1.29 (0.85, 1.95)	3.24 (2.27, 4.63)	2.03 (1.33, 3.11)[c]
Spied-upon	2.03 (1.79, 2.30)	1.35 (1.17, 1.56)[b]	2.66 (2.36, 3.00)	1.56 (1.36, 1.78)[b]
Hearing voices	1.96 (1.76, 2.17)	1.26 (1.12, 1.42)[b]	2.24 (2.02, 2.47)	1.38 (1.23, 1.54)[b]
Somatic ideation	2.10 (1.68, 2.62)	1.06 (0.82, 1.38)	2.93 (2.34, 3.65)	1.46 (1.13, 1.88)[c]

In each section, the missing data have been excluded from the statistical analyses.
[a] Odds ratio adjusted for sex, age, drug and alcohol usage, violence from adults, being bullied, and GHQ total score.
[b] $p<0.001$.
[c] $p<0.01$.

Blitstein et al., 2005; Spidel et al., 2010). The study also revealed that particular types of PLEs ('spied-upon' and 'voice hearing') are significantly associated with interpersonal violence, while others are not significantly related to this type of violent behavior. On the other hand, all of the types of PLEs assessed in this study were significantly associated with violence towards objects.

These results suggest that PLEs may contribute to violent behavior, and that such behavior in individuals with schizophrenia may be at least partially explained by the continuum hypothesis (Stip and Letourneau, 2009; van Os et al., 2000; Verdoux and van Os, 2002). This is when violent behavior is not directly caused by a psychotic disorder as a discrete entity, but is mediated by the psychotic symptoms which exist on a continuum from normal experiences. In other words, violence in individuals diagnosed with psychotic disorders may share an etiological background with such behavior in the general population. Accordingly, early detection and intervention targeted at PLEs may be needed to prevent the harmful behaviors by adolescents with these experiences.

Mojtabai (2006) suggested that PLEs are associated with interpersonal violence in a dose–responsive manner in the general population. Our results have confirmed that the same association exists in adolescents, even when possible confounding factors are controlled for by conducting a multivariate binary logistic regression analysis.

Table 4
Effects of a combination of delusional and hallucinatory experiences on violence.

	Adjusted OR[a] for interpersonal violence (95%CI)	Adjusted OR[a] for violence towards objects (95%CI)
Delusional score of PLE[b]	1.31 (1.15, 1.50)[c]	1.49 (1.31, 1.70)[c]
Voice hearing	1.34 (1.17, 1.54)[c]	1.33 (1.17, 1.51)[c]
Interaction term for delusional score of PLE and voice hearing	0.72 (0.60, 0.86)[d]	0.77 (0.64, 0.93)[d]

In each section, the missing data have been excluded from the statistical analyses.
[a] Odds ratio adjusted for sex, age, drug and alcohol usage, violence from adults, being bullied, and GHQ total score.
[b] ORs were calculated for a one point increase in the delusional score of PLE.
[c] $p<0.001$.
[d] $p<0.01$.

Previous studies have reported that a particular sub-group of delusions, which provoke threat and control override characteristics, represents an important risk factor for violence in both the general population and a number of patient groups (Link et al., 1998; Cheung et al., 1997; Swanson et al., 2006). Our data suggests that when it comes to adolescents, this conclusion can only be applied to interpersonal violence, but not to violent behavior towards objects. Moreover, the present study also suggests that subclinical auditory hallucinations may be an important risk factor for the two types of violence in this population. Conceivably, the association between voice hearing and interpersonal violence is mediated by the threat and control override characteristics displayed in the contents of this type of experience. However, the same explanation cannot be applicable to the association between voice hearing and violence towards objects, because all of the other PLEs, including those without threat and control override characteristics, were proved to be significantly associated with this type of violent behavior.

This discrepancy between interpersonal violence and violence towards objects implies that threat and control override characteristics of delusions or hallucinations are not needed to induce violent behavior. This theory could be validated by the findings by Teixeira and Dalgalarrondo (2009) suggesting that delusional patients who are frightened or who have other negative affects related to delusional ideas appear to commit fewer violent acts. If this is the case, then some unknown factors such as accompanying anxiety might determine the significance of each type of PLEs in provoking violence. It may well be the unknown factors that may define the three major roles of psychosis in inducing violence: 1. in focusing (organizing) decision and behavior, giving individuals a clear motivation for violence, 2. in destabilizing (disorganizing) decisions and behavior, interfering with the ability of individuals to manage interpersonal conflicts, and 3. disinhibiting role in violence (Douglas et al., 2009).

Contrary to an indication in a previous study using a resident sample of high security hospital patients (Taylor et al., 1998), a combination of delusional and hallucinatory experiences did not seem more significantly associated with violent behavior than either alone in the community sample of adolescence. The difference in the characteristics of the samples might lead to this discrepancy.

There are several limitations with this research. Firstly, our survey was cross-sectional, meaning that there may be

some respondents for whom violence occurred before the onset of their PLEs. Accordingly, it is impossible to demonstrate an actual causal relationship between PLEs and violent behavior. In other words, the results in the present study could be interpreted as meaning that violent behavior could predict PLEs. Indeed, Gosden et al. (2005) demonstrated that violence predicts the diagnosis of schizophrenia. Nevertheless, in the questionnaire used in our survey, the participants were told that they should base their answers about PLEs on whether they had ever experienced these symptoms at any point in their life, while information about interpersonal violence and violence towards objects was based on experiences in the previous year. This design of questionnaire could increase the possibility that PLEs temporally precede the occurrence of violent behavior.

Secondly, the two types of violent behavior were only assessed by self-reporting on the part of the participants, and not by informant reports. Self-reported violence may lead to misclassification and an under or over-estimation of the prevalence of these behaviors. Nevertheless, there is evidence that self-reports of violence correspond reasonably well with administrative records (Crisanti et al., 2005), as described in Section 2.2.2. Though Stompe et al. (2004) suggested that the threat/control override factor of delusion was not associated with violence but with severity thereof, we could not re-examine these findings with our data, because we did not evaluate the seriousness of the violent behavior.

Thirdly, as this was a school-based survey, we were unable to obtain answers from absent students. Yet, violent behavior and/or PLEs may be more prevalent among those who are frequently absent from school, as well as those who have been off for a long time. Accordingly, an association between violence and PLEs in this study may well be under or over-estimated.

Fourthly, we did not include a number of relevant factors (i.e. conduct disorder, oppositional defiant disorder, antisocial personality disorder and socioeconomic status) in the potential confounding factors. Though these factors have been demonstrated to be important predictors of violence in psychotic people (Douglas et al., 2009; Coid et al., 2006; Goethals et al., 2008), no assessment was done with regard to these variables in our survey.

In addition, because of the very large sample size, even a small amount of difference could be shown statistically significant. Moreover, we cannot exclude the possibility that some portion of participants may be prodromal for or diagnosed with schizophrenia.

In conclusion, PLEs may predict both interpersonal violence and violence towards objects in adolescents. Of the five types of psychotic-like experiences considered, those of 'being spied-upon' and 'voice hearing' were particularly associated with interpersonal violence, while all of the assessed PLEs were significantly related to violence towards objects. Consequently, early detection and intervention for PLEs may be needed before they lead to harmful behavior. Additionally, violent acts by individuals with schizophrenia may not be a direct consequence of the disease itself, but may instead share an etiological background with such behavior in the general population. Further investigations could be conducted to give a clearer picture of the mechanism which links PLEs to violent behavior in adolescents.

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Contributors

Dr. Y. Kinoshita designed the study, undertook the statistical analysis, and interpreted the data. Drs. Nishida, Sasaki and Okazaki designed the study and wrote the protocol. Drs. Nishida and Shimodera collected the data. Drs. Y. Kinoshita and Furukawa wrote the first draft of the manuscript. Dr. K. Kinoshita managed the literature searches. Drs. K. Kinoshita, Watanabe, Akechi, Oshima and Inoue revised the first draft critically. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflict of interest.

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Relative indices of treatment effect may be constant across different definitions of response in schizophrenia trials

Toshi A. Furukawa [a,b,*], Tatsuo Akechi [b], Stefan Wagenpfeil [c], Stefan Leucht [d]

[a] Department of Health Promotion and Human Behavior (Cognitive–Behavioral Medicine), Kyoto University Graduate School of Medicine/School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan
[b] Department of Psychiatry and Cognitive–Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan
[c] Institute of Medical Statistics and Epidemiology of the Technische Universität München, Klinikum rechts der Isar, Ismaningerstr. 22, Munich 81675, Germany
[d] Department of Psychiatry and Psychotherapy, Technische Universität München, Klinikum rechts der Isar, Ismaningerstr. 22, Munich 81675, Germany

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ABSTRACT

Background: In randomized controlled trials of antipsychotics, various cutoffs have been used to define response on continuous outcome measures.
Aims: To find a summary effect measure that remains constant across different definitions of response.
Method: We conducted secondary analyses of individual patient data from 10 randomized controlled trials of second-generation antipsychotics for schizophrenia (n = 4278) by applying a meta-analytic approach to produce odds ratios (OR), risk ratios (RR) and risk differences (RD) and their 95% confidence intervals (CI) for different definitions of response, using cutoffs of 10% through 90% reduction on the symptom severity rating scales. Constancy of these indices was examined through visual inspection, by way of I-squared statistics to quantify heterogeneity, and by way of coefficients of variation. If any of these indices were found to remain reasonably constant, we next examined the concordance between the number needed to treat (NNT) predicted from them and the observed NNT.
Results: OR and RR remained reasonably constant across various definitions of response, especially for those using thresholds of 10% through 70% reduction. The NNTs predicted from OR and RR agreed well with the observed NNTs, with ANOVA intraclass correlation coefficients of 0.96 (95% CI: 0.92 to 0.98) and 0.86 (0.72 to 0.93), respectively.
Conclusions: The relative measures of treatment effectiveness remain reasonably constant across different scale-derived definitions of response and, in conjunction with varying control event rates, can give accurate estimates of NNTs for individuals with schizophrenia.

1. Introduction

In psychiatry "hard" outcomes such as death are not readily available or appropriate indices of treatment effectiveness. Instead, continuous outcomes based on rating scales are often employed but it is sometimes not easy to interpret the meaning of these scores (Norman et al., 2001). For example, in a hypothetical drug trial of acute phase treatment of schizophrenia, a statistically significant difference on a certain disease severity measure of 70 vs 80 may be reported for the drug and placebo arms, respectively, at the end of the trial. However, what these 70 or 80, or what this 10-point difference, on this scale mean clinically may often not be transparent.

On the other hand, a categorical approach can be more interpretable, for example, if the response or remission rates

* Corresponding author. Department of Health Promotion and Human Behavior (Cognitive–Behavioral Medicine), Kyoto University Graduate School of Medicine/School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan. Tel.: +81 75 753 8291; fax: +81 75 753 4641.
E-mail address: furukawa@kuhp.kyoto-u.ac.jp (T.A. Furukawa).

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are reported to be 50% vs 30% in the two arms. Trialists have therefore often included "response" rates defined as a threshold decrease on the continuous outcome (Altman and Royston, 2006). Unfortunately, for many of these continuous outcomes, there usually is no validated or even agreed-upon cutoff to define "response." In the case of schizophrenia trials, the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) are the two most frequently used scales but investigators have used various percentage improvements from 20% through 50% to define response (Beasley et al., 1996b; Marder and Meibach, 1994; Peuskens and Link, 1997; Small et al., 1997).

Such lack of consensus in the definition of response poses several related difficulties. First, there is suspicion that the trialists choose their cutoff not because it is clinically appropriate but because it is more likely to result in "statistically significant" differences. In recent reports of schizophrenia trials there is a tendency to use 20% reduction as a cutoff, apparently in the belief that a lower cutoff increases the ability to find statistically significant differences between drugs. However, 20% reduction represents something less than "minimal improvement" (Leucht et al., 2005a, b). A statistically significant difference in the rates of patients showing borderline or greater improvement (but not necessarily in moderate or greater improvement) would certainly not be clinically meaningful. Second, in order to obtain unbiased and generalizable estimates of the true treatment effects, we need comprehensive meta-analyses of relevant trials. However, if "response" is defined variably across different trials addressing a similar clinical question, we cannot be sure if we could safely combine them in a meta-analysis.

These problems would be greatly ameliorated if one could find a measure of effect that remained more or less constant across a range of thresholds. The odds ratio (OR), relative risk (RR) and risk difference (RD) or its inverse, the number needed to treat (NNT), are the representative indices of treatment effectiveness for dichotomous outcomes. When the outcome is dichotomous, the results of a trial can be summarized as in the following 2*2 table.

	Response	Non-response
Treatment	a	b
Control	c	d

The more clinically interpretable indices are RR and RD. RR is the ratio of the response rates in the treatment and control arms; it is therefore $(a/(a+b))/(c/(c+d))$. RD is the difference in the response rates in the treatment and control arms; it is therefore $a/(a+b)-c/(c+d)$. NNT, which is the inverse of RD, shows the number of patients one would need to treat in order to have one more response in the treatment arm that would not have happened if on the control arm. It therefore nicely summarizes the amount of effort that both clinicians and patients need to expend in order to obtain one more response. For example, a treatment that produces a response rate of 50% in comparison with a placebo response rate of 30% would be translated into an NNT of $1/(0.5-0.3)=5$. In other words, one would need to treat 5 patients in order to produce one more responder over what would have happened on placebo. On the other hand, OR is intuitively difficult to understand because it is the ratio of the odds of showing response over not showing response in the treatment and control arms; hence it is (a/b)/(c/d) or ad/bc. OR, however, has some strong mathematical properties because OR of non-response is the inverse of OR of response, whereas such a relationship does not hold for RR (Deeks, 2002).

In the following analyses, we examined individual patient data from several clinical trials of schizophrenia to see if any of OR, RR or RD may remain constant across different definitions of response, so that it can be used as the generalizable index of treatment effectiveness.

2. Methods

2.1. Database

Individual patient data from 10 trials comparing olanzapine vs haloperidol (5 comparisons, baseline n=2974) (Beasley et al., 1996b, 1997; Keefe et al., 2006; Lieberman et al., 2003; Tollefson et al., 1997), amisulpride vs haloperidol (4 comparisons, baseline n=1198) (Carriere et al., 2000; Colonna et al., 2000; Moller et al., 1997; Puech et al., 1998), and olanzapine vs placebo (2 comparisons, baseline n=502) (Beasley et al., 1996a,b) that administered either the BPRS or PANSS were reanalyzed *post hoc*. These 10 trials were selected from among the 13 trials that compared olanzapine and 7 trials that compared amisulpride against various other antipsychotics or placebo and that had been provided to us by respective manufacturers, when they compared olanzapine vs haloperidol, amisulpride vs haloperidol or olanzapine vs placebo because these were the only comparisons that resulted in statistically significant differences between the compared arms when meta-analyzed. Working with non-significant ORs, RRs or RDs would not reveal their differential performances. One trial was a three-armed trial among olanzapine, haloperidol and placebo, and contributed to two comparisons. Table 1 summarizes important characteristics of the included studies.

All studies were randomized and all but one (Colonna et al., 2000) was described as double-blind. All amisulpride studies and one olanzapine study (Beasley et al., 1996b) used the original BPRS, and all the other olanzapine studies used PANSS. For the latter studies we calculated the PANSS-derived BPRS scores because PANSS includes all items of the BPRS. The BPRS is a clinician-rated rating scale designed to measure change in psychopathology and contains 18 items, each of which is rated on a seven-point scale ranging between 1="not present" and 7="extremely severe," resulting in a total score between 18 and 126 (Overall and Gorham, 1962). The PANSS was developed to improve on the BPRS by including all its items and by adding 12 more items to cover broader psychopathology; its score therefore ranges between 30 and 210 (Kay et al., 1987).

For fixed-dose studies, we selected only those arms with optimum doses of second-generation antipsychotic drugs as reported in dose-finding studies (amisulpride 400–800 mg/day, olanzapine 10–20 mg/day and risperidone 4–6 mg/day) (Leucht et al., 2009). We therefore excluded 61 participants from Puech et al. (1998) who had received a potentially

Table 1
Characteristics of the included studies.

Study	Antipsychotic drugs and daily dosage (mg)	Sample size (n)	Duration (weeks)	Mean BPRS at baseline	Selected patient characteristics
Möller et al. 1997 (Moller et al., 1997)	Amisulpride 600–800	95	6	61.7	Inpatients with paranoid, disorganized or undifferentiated schizophrenia (DSM-III-R), BPRS psychotic subscore ≥12 and at least two BPRS psychosis items ≥4
	Haloperidol 15–20	96			
Puech et al. 1998 (Puech et al., 1998)	Amisulpride 400–1200	194	4	61.3	Inpatients with acute exacerbations of paranoid, disorganized or undifferentiated schizophrenia (DSM-III-R), BPRS psychotic subscore ≥12 and at least two BPRS psychosis items ≥4
	Haloperidol 16	64			
Colonna et al. 2000 (Colonna et al., 2000)	Amisulpride 200–800	368	51	56.2	In- or outpatients with acute exacerbations of paranoid, disorganized or undifferentiated schizophrenia (DSM-III-R), at least two BPRS psychosis items ≥4
	Haloperidol 5–20	118			
Carrière et al. 2000 (Carriere et al., 2000)	Amisulpride 400–1200	97	17	65.4	Inpatients with paranoid schizophrenia or schizophreniform disorder (DSM-IV)
	Haloperidol 10–30	105			
Beasley et al. 1997 (Beasley et al., 1997)	Olanzapine 10–15	175	6	59.1	Inpatients with acute exacerbations of schizophrenia (DSM-III-R), BPRS total score ≥42, CGI-S ≥4
	Haloperidol 15	81			
Tollefson et al. 1997 (Tollefson et al., 1997)	Olanzapine 5–20	1337	6	51.5	In- and outpatients with schizophrenia, schizophreniform or schizoaffective disorder (DSM-III-R), BPRS total score ≥36
	Haloperidol 5–20	659			
Lieberman et al. 2003 (Lieberman et al., 2003)	Olanzapine 5–20	131	12	46.8	In- and outpatients with a first episode of schizophrenia, schizophreniform or schizoaffective disorder (DSM-IV), at least two PANSS psychosis tems ≥4, CGI-S ≥4
	Haloperidol 2–20	132			
Keefe et al. 2006 (Keefe et al., 2006)	Olanzapine 5–20	159	8	48.4	In- and outpatients with schizophrenia or schizoaffectivedisorder according to DSM-IV, BPRS total score ≥36, at least two PANSS psychosis items ≥4
	Haloperidol 2–19	97			
Beasley et al. 1996 (Beasley et al., 1996b)	Olanzapine 10–15	133	6	59.9	Inpatients with acute exacerbations of schizophrenia (DSM-III-R), BPRS total score ≥42, CGI-S ≥4
	Aloperidol 15	69			
	Placebo	68			
Beasley et al. 1996 (Beasley et al., 1996a)	Olanzapine 10	50	6	55.2	Inpatients with schizophrenia (residual type excluded) (DSM-III-R), BPRS total score ≥42, CGI-S ≥4
	Placebo	50			

BPRS: Brief Psychiatric Rating Scale, CGI-S: Clinical Global Impression Severity Scale, DSM: Diagnostic and Statistical Manual of Mental Disorders, and PANSS: Positive and Negative Syndrome Scale.

subtherapeutic 100 mg/day of amisulpride, 175 participants from Beasley et al. (1997) who received 5 mg/day or 1 mg/day of olanzapine, 65 participants from Beasley et al. (1996b) who were given 5 mg/day of olanzapine and 52 participants from Beasley et al. (1996a) who received 1 mg/day of olanzapine. The active comparator, haloperidol, was given in a fixed dose of 15 mg/day or 16 mg/day or in variable dosage ranging between 2 and 30 mg/day: these dosages have been found to show similar effectiveness (Leucht et al., 2009; Waraich et al., 2002).

The mean BPRS total score of the included participants was 54.3 (SD = 10.8) at baseline, which would correspond with the "markedly ill" range (Leucht et al., 2005a). There were 2895 men and 1383 women. Their mean age was 36.6 (10.5) years, weight 75.5 (16.4) kg and height 171.6 (9.6) cm.

2.2. Statistical analyses

We first calculated the numbers of responders defined as 10% through 90% reduction on the BPRS or PANSS total score at 4 weeks, with missing data supplemented by the last-observation-carried-forward (LOCF) method even if a participant dropped out before the first post-baseline rating. The percentage reduction was calculated according to the formulae: $B\% = (B_0 - B_{4LOCF}) * 100/(B_0 - 18)$ for BPRS and $P\% = (P_0 - P_{4LOCF}) * 100/(P_0 - 30)$ for PANSS, where B_0 and P_0 are BPRS and PANSS scores at baseline and B_{4LOCF} and P_{4LOCF} are respective scores at 4 weeks with LOCF, because 18 and 30 are the minimum scores for BPRS and PANSS, respectively, according to the original rating system (Kay et al., 1987; Overall and Gorham, 1962).

We then ran meta-analyses of response rates defined as 10% through 90% reduction for each comparison in terms of OR, RR and RD, using the Review Manager software by the Cochrane Collaboration (2008). Because we are looking for a single index that may remain constant through different definitions of response, we used the Mantel–Haenszel fixed effect model (Mantel and Haenszel, 1959). However, in order to examine robustness of our findings, we repeated the same analyses based on the DerSimonian random effects model (DerSimonian and Laird, 1986).

The constancy of these three summary indices of treatment effectiveness was examined (i) through visual inspection of the obtained indices and their 95% confidence intervals, (ii) I-squared statistics of the hypothetical meta-analyses of the relevant trials adopting different thresholds for 10% through 90%, and (iii) coefficient of variation (CV). CV is defined as SD/|mean|, and its 95% confidence intervals were calculated according to Johnson & Welch (1939). Because heterogeneity may arise from differences in the baseline severity of the included patients, study year and/or methodologic rigor of the included trials, we repeated the analyses by excluding trials that had low baseline BPRS scores (Keefe et al., 2006; Lieberman et al., 2003; Tollefson et al., 1997), old trials before year 2000 (Beasley et al., 1996a,b, 1997; Moller et al., 1997; Puech et al., 1998; Tollefson et al., 1997) or non-blinded trials (Colonna et al., 2000).

If any of OR, RR and RD appeared constant through ranges of definitions of response and may therefore be given the role of the representative index of effectiveness of one arm over the other regardless of the cutoffs in the continuous scale, we then examined if that summary effect measure can accurately

predict the other effect measures according to the known mathematical relationships among OR, RR and RD on one hand and control event rate (CER; the response rate in the control group) on the other. Given the 2*2 table as shown in the Introduction, by introducing CER=c/(c+d), we can calculate RR and RD from OR using the formulae:

$$RR = OR / (1-CER + CER*OR)$$

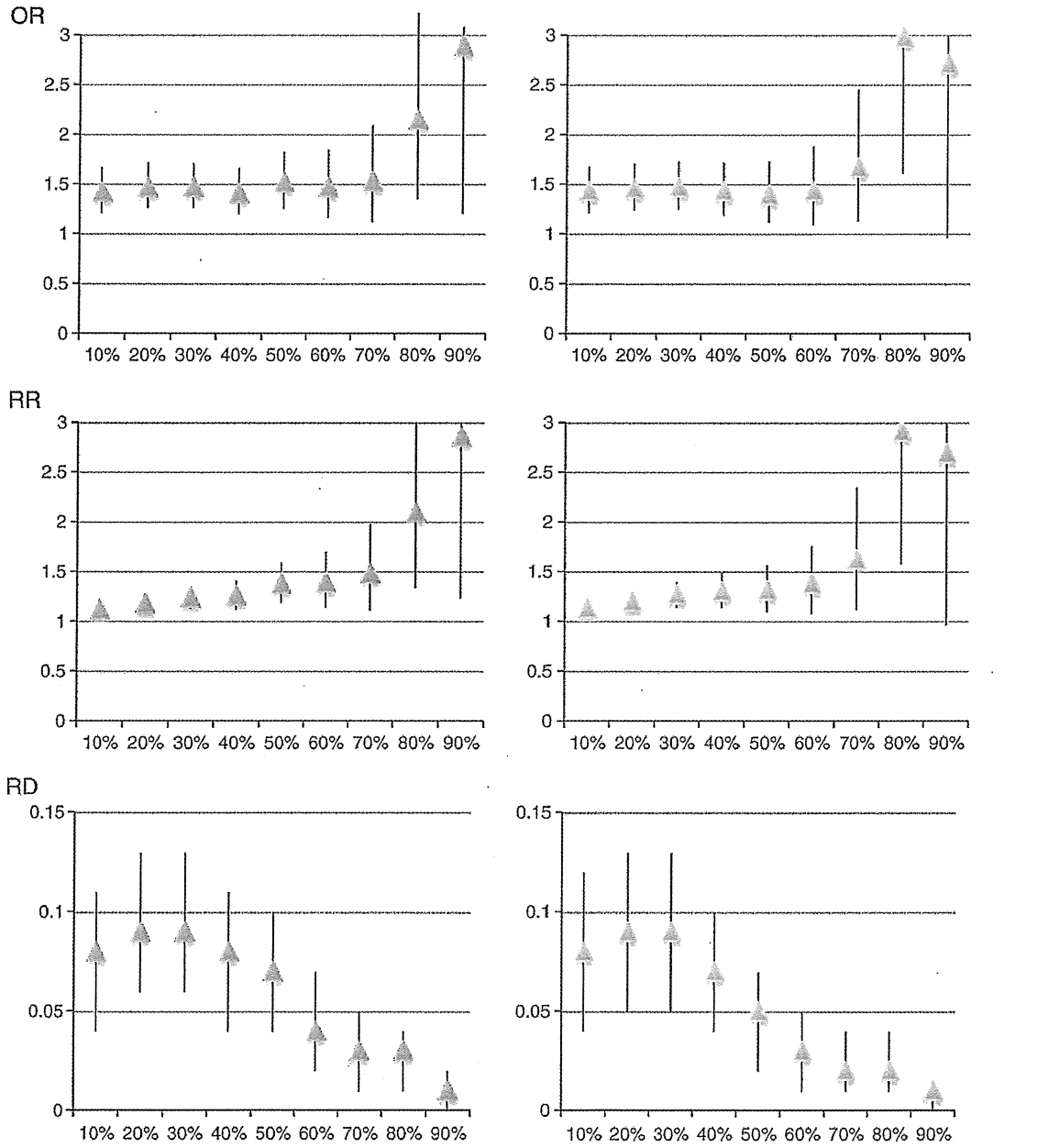
$$RD = CER*(RR-1).$$

We can also calculate OR and RD from RR using the same formulae. The degree of absolute agreement between the observed values and the predicted values was expressed by way of two-way mixed ANOVA intraclass coefficient (ICC) for absolute agreement.

3. Results

3.1. Visual inspection of the constancy of OR, RR and RD across different definitions of response

Figs. 1, 2 and 3 depict the OR, RR and RD corresponding to the various definitions of response using 10% through 90% reduction in the BPRS or PANSS total scores for the comparisons olanzapine vs haloperidol, amisulpride vs



The left column (green triangles) is based on BPRS, and the right column (blue triangles) represents PANSS.

Fig. 1. Olanzapine vs haloperidol.

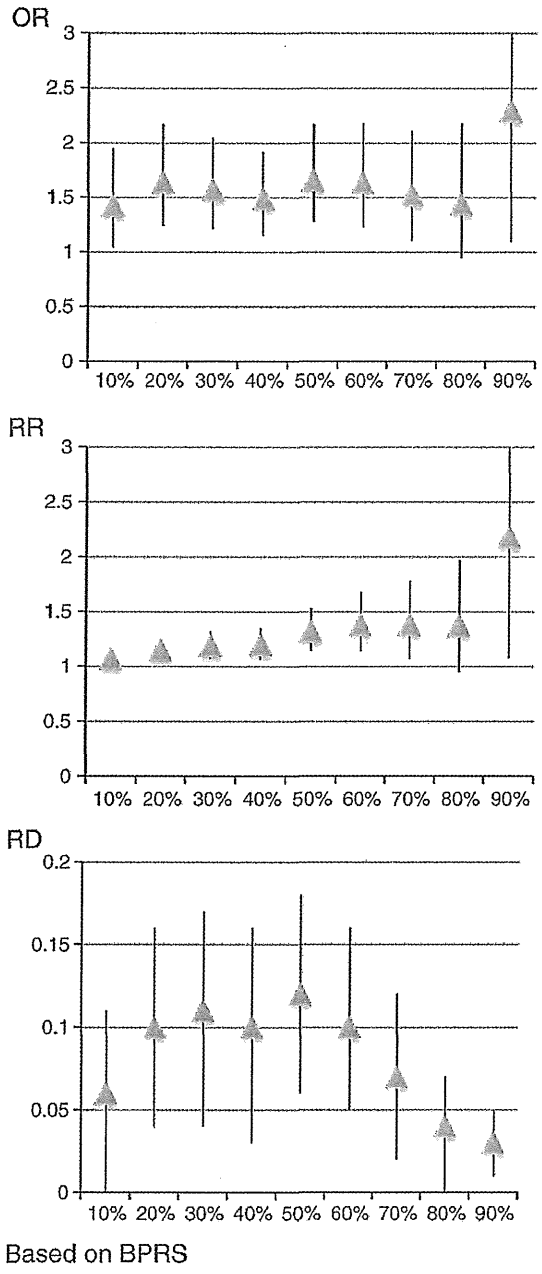


Fig. 2. Amisulpride vs haloperidol.

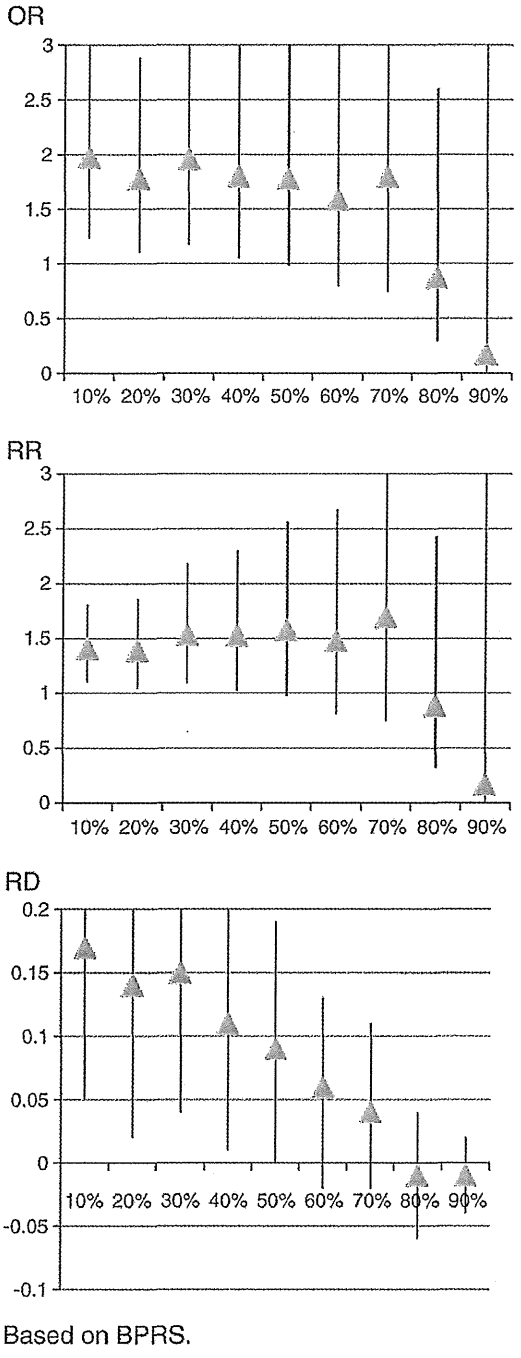


Fig. 3. Olanzapine vs placebo.

haloperidol and olanzapine vs placebo, respectively. Visual inspection of these graphs indicates that both OR and RR appear to remain relatively constant, especially for the ranges of 10% through 70% reduction.

For the extreme ranges of 80% or 90% reduction, there were too few participants to achieve the so-defined response and the calculated OR and RR were all unstable and resulted in wide 95% confidence intervals.

3.2. Numerical examination of constancy of OR, RR and RD

Table 2 lists the I-squared for the hypothetical pooling across all definitions of response, and CV for the OR, RR and RD.

RD produced I-squared statistics which would be interpreted as representing moderate to high heterogeneity (Higgins et al., 2003) and were always greater in absolute value than those for RR, which were then greater than those for OR, although neither of these differences was statistically significant (Wilcoxon signed rank test). Focusing on more homogeneous trials by excluding trials with low baseline BPRS scores, old trials or non-blinded trials resulted in very similar I-squared values (Table 2).

RD also had the greatest CV, while OR had the smallest CV: the differences in CV between RD on one hand and OR or RR

Table 2
Numerical examination of constancy of OR, RR and RD.

	Comparison	Scale	I-squared				CV
			All	Excl. low BPRS trials	Excl. old trials	Excl. non-blinded trial	
OR	olanzapine vs haloperidol	BPRS	13%	3%	0%	3%	0.29 (0.23 to 0.38)
		PANSS	0%	0%	0%	0%	
	amisulpride vs haloperidol	BPRS	0%	0%	0%	0%	
	olanzapine vs placebo	BPRS	0%	0%	0%	0%	
RR	olanzapine vs haloperidol	BPRS	43%	11%	0%	43%	0.33 (0.27 to 0.44)
		PANSS	11%	13%	0%	11%	
	amisulpride vs haloperidol	BPRS	2%	2%	21%	0%	
	olanzapine vs placebo	BPRS	0%	0%	0%	0%	
RD	olanzapine vs haloperidol	BPRS	82%	20%	60%	82%	0.62 (0.55 to 0.71)
		PANSS	86%	76%	47%	86%	
	amisulpride vs haloperidol	BPRS	43%	43%	58%	35%	
	olanzapine vs placebo	BPRS	76%	76%	86%	76%	

on the other were both statistically significant, because their 95% CIs did not overlap.

3.3. Which relative index of treatment effect enables more accurate prediction of treatment effect on the other indices, OR or RR?

It now appears that both OR and RR remain relatively constant through ranges of definitions of response on the continuous scale, especially for 10% through 70% where we have non-small control event rates. The next question then is which of these can allow more accurate prediction of treatment effect according to the other indices, when we apply the mathematical formulae as explained in the Methods section. As the observed OR and RR, we took the average of the values for 10% through 70% reduction, as these appeared to remain particularly constant in Figs. 1 through 3.

Using this OR and the varying control event rates, the ANOVA ICC (two-way mixed, absolute agreement) between the observed and the predicted RRs, RDs and NNTs was 0.94 (0.87 to 0.97), 0.95 (0.90 to 0.98) and 0.96 (0.92 to 0.98) respectively for the ranges between 10% through 70%.

With regard to the RR, the ANOVA ICC between the observed and the predicted ORs, RDs and NNTs was −0.03 (−0.37 to 0.34), 0.61 (0.31 to 0.80) and 0.86 (0.72 to 0.93) respectively.

3.4. Sensitivity analyses

All the analyses based on random effects model were essentially unchanged. For example, the ANOVA ICCs between the RR, RD and NNT predicted from OR and those actually observed were 0.93 (0.85 to 0.97), 0.95 (0.90 to 0.98) and 0.91 (0.82 to 0.96) respectively for the ranges between 10% and 70%. The corresponding ICCs between the OR, RD and NNT predicted from RR and those actually observed were −0.01 (−0.37 to 0.35), 0.59 (0.27 to 0.79) and 0.71 (0.47 to 0.86). Once again, assuming constancy of OR enabled excellent prediction of RR, RD and NNT in conjunction with varying control event rates, while assuming constancy of RR enabled satisfactory prediction of NNT.

4. Discussion

Based on individual patient data of 4278 patients with schizophrenia participating in trials of acute phase antipsychotic treatment, we examined empirically whether OR, RR or RD remains constant across different definitions of response on the BPRS and the PANSS. We found that both OR and RR remain relatively constant across plausible ranges of definitions of response and that OR, in particular, was able to predict RR, RD and NNT very accurately using mathematical formulae and estimates of the control event rate.

The greater generalizability of relative measures of treatment effectiveness (such as OR and RR) over absolute ones (such as RD and NNT) is consistent with previous studies. Using a random subset of meta-analyses contained in the Cochrane Library, Furukawa et al. (2002) examined the concordance between treatment indices of each RCT included in a meta-analysis and the meta-analyzed results of all the other RCTs. OR and RR showed the highest concordance rates, even when the control event rate differed substantially, while the concordance for RD was much lower. In other words, OR and RR appeared more generalizable than RD, regardless of the control event rate.

One of the central goals of evidence-based medicine, to individualize group data from clinical research to match each individual patient's values and preferences, seems therefore to have found some empirical ground here (Sackett, 2001). By assuming a constant relative index of treatment effectiveness, either in terms of OR or RR, and by combining it with each patient's expected event rate when given the control intervention, we can estimate individualized NNT using mathematical formulae as explained in the Methods of this paper. In other words, when the relative difference in effect is constant, the absolute difference in effect will be different, depending on the expected control event rate that can vary from patient to patient.

The present study has added support that relative indices of treatment may be generalizable even across a range of scale-derived definitions of response. In other words, because the relative effectiveness is constant across different thresholds, the absolute effectiveness can be calculated taking into account the threshold that the patient wishes to achieve. For example, the OR of olanzapine over haloperidol to bring about a response in the acute phase treatment of schizophrenia is

approximately 1.5 for various definitions of response of 10% through 70% reductions on the BPRS or PANSS (Cf. Fig. 1). However, olanzapine causes more significant weight gain than haloperidol, with an NNH estimated to be around 6 (95% CI: 4–11) (Duggan et al., 2005). A patient who is normo- to underweight now and who does not have any family and other risk factors for obesity may be happy to try olanzapine to achieve a 30% or more decrease in disease severity. For this patient, given an estimate that approximately 40% of the patients would achieve 30% or more reduction on placebo, NNT will be calculated to be 9 and he or she may find this NNT as small as NNH for weight gain to justify treatment with olanzapine. On the other hand, another patient who is already somewhat overweight and has multiple family history of diabetes mellitus and cardiovascular diseases may like 70% or more decrease in the BPRS before he/she selects olanzapine over haloperidol. However, because the control event rate for 70% reduction could be as low as 6% and the corresponding NNT may be as large as 50, he/she might reason that trying olanzapine may not be worthwhile.

Several caveats are in order before we conclude. First, we do not yet know if the current results would apply to other continuous outcomes in other areas of psychiatry or medicine. In fact there is no mathematical necessity for one measure of effect to be stable across thresholds in all settings, as performance of summary effect measures would be dependent on the underlying distribution of the continuous outcomes. However, some sporadic examples we find in the literature suggest that the present findings may apply in other areas as well. Among patients with active rheumatoid arthritis refractory to tumor necrosis factor α, abatacept was superior to placebo in bringing about ACR 20% responses with an OR of 4.2 (95% CI: 2.6 to 6.9), ACR 50% responses with an OR of 6.5 (2.5 to 17), and ACR 70% responses with an OR of 7.4 (1.7 to 32) (Genovese et al., 2005). For patients with psoriasis, ustekinumab, a human interleukin-12/23 monoclonal antibody, beat placebo in reducing the Psoriasis Area and Severity Index by at least 50% (OR=45, 95% CI: 26 to 75), by at least 75% (OR=63, 30 to 133) and by at least 90% (OR=36, 14 to 89) (Leonardi et al., 2008). Thus in both studies, ORs for different thresholds showed largely overlapping confidence intervals that contained all the reported point estimates. More definitive analyses would require individual patient data from more studies, and the present study was the first to carry out such an examination in the context of second-generation antipsychotic trials for people with schizophrenia.

Second, the individual patient data that we had access to did not include important individual patient characteristics such as duration of untreated psychosis, years ill, treatment history or concurrent psychosocial treatments. How these variables could have moderated the present results is hard to predict. However, if the present results are generalizable, we could expect that OR and RR would remain relatively constant within each prognostic stratum as defined by such baseline characteristics. Third, the included studies are limited to trials around 2000. If the present results would apply to more recent trials, especially in view of the changes in patient selection and given increasing number of failed placebo-controlled trials recently, awaits replication.

Taking all these considerations into account, we think that our results have several important implications for research. First, we can safely combine trials that adopted different definitions of response in a meta-analysis to derive the pooled OR or RR, which can then be applied to wider ranges of response definitions and of patients. Second, in the original report of a clinical trial, however, it will be more informative not only to report the OR or RR but also the control event rates for different definitions of response (Leucht et al., 2007). Third, when we plan an RCT, given the constant OR, mathematics shows that the threshold at which the response rate approaches 50% will provide the greatest statistical power.

The implication of the present study for clinical practices is straightforward. The constant OR across different scale-derived definitions of response, in conjunction with varying control event rates, will give accurate estimates of individualized NNTs in pharmacotherapy of schizophrenia and possibly in other areas of medicine. The RR also remains relatively constant so that it may be used, in conjunction with varying control event rates, to estimate NNTs. Using RR has the advantage of allowing busy clinicians easier calculation than using OR.

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Contributors

TAF conceived the study. TAF, SW and SL undertook the statistical analyses. TAF wrote the first draft of the manuscript. TA, SW and SL provided essential critical comments. All the authors have approved the final manuscript.

Conflict of interest

TAF received research funds and speaking fees from Astellas, Dai-Nippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Meiji, Otsuka, Pfizer and Schering–Plough. TA received research funds and speaking feeds from Astellas, AstraZeneca, BMS, Daiichi-Sankyo, Dai-Nippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Kyowa-Hakko, Meiji, Otsuka, Pfizer, SanofiAventis, Shionogi and Yakult. SW has no conflict of interest to declare. SL received speaker/consultancy/advisory board honoraria from SanofiAventis, BMS, Eli Lilly, Essex Pharma, AstraZeneca, GlaxoSmithKline, Janssen/Johnson and Johnson, Lundbeck and Pfizer. SanofiAventis and EliLilly supported research projects by SL.

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CASE REPORT

Social anxiety disorder as a hidden psychiatric comorbidity among cancer patients

TATSUO AKECHI, M.D., PH.D., TORU OKUYAMA, M.D., PH.D., RYUICHI SAGAWA, M.D., PH.D., MEGUMI UCHIDA, M.D., TOMOHIRO NAKAGUCHI, M.D., YOSHINORI ITO, M.S., AND TOSHIAKI A. FURUKAWA, M.D., PH.D.

Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya, Aichi, Japan

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ABSTRACT

Objective: Social anxiety disorder is one of the most popular psychiatric disorders in the general population and is also well known as a very common comorbid psychiatric disorder among patients with major depression. On the other hand, social anxiety disorder has been termed "the neglected anxiety disorder" because its diagnosis is often missed. Furthermore, the potential impact of social anxiety disorder on the psychological distress of cancer patients has not been reported.

Method: We encountered two cancer patients with refractory depression after cancer diagnosis, in whom comorbid social anxiety disorder was unexpectedly detected during a subsequent follow-up.

Results: To the best of our knowledge, this is the first report to discuss the potential impact of social anxiety disorder on cancer patients' distress. These two cases may help to improve our understanding of the complicated mental health problems of cancer patients and the potential influence of social anxiety disorder on patients' follow-up medical treatment.

Significance of results: Comorbid social anxiety disorder should be considered when a cancer patient's depression is resistant to treatment and the existence of communication problems between the patient and the medical staff is suspected.

KEYWORDS: Oncology, Depression, Social anxiety disorder, Comorbidity

INTRODUCTION

Social anxiety disorder is one of the most popular psychiatric disorders in the general population, and previous epidemiological studies have indicated that the lifetime prevalence of this disorder is >10% (Stein & Stein, 2008). Social anxiety disorder is also well-known as the most common comorbid psychiatric disorder among patients with major depression (Zimmerman & Chelminski, 2003). On the other hand, social anxiety disorder has been termed "the neglected anxiety disorder" because its diagnosis is often missed (Liebowitz, 1999).

We experienced two cancer patients who became depressed after being diagnosed with cancer and who did not respond to antidepressive treatment; comorbid social anxiety disorder was unexpectedly detected during a subsequent follow-up examination in both of these patients. To the best of our knowledge, the potential impact of social anxiety disorder on the distress of cancer patients has not been previously reported. Here, we report the two abovementioned cases in the hope of advancing our understanding of cancer patients' complicated mental health problems and the potential influence of

Address correspondence and reprint requests to: Tatsuo Akechi, Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya, Aichi, 467-8601 Japan. E-mail: takechi@med.nagoya-cu.ac.jp