Acceptability of transdermal antipsychotic patches by patients who refuse oral medication and their effectiveness in preventing recurrence of delirium: a retrospective observational study

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Injectable antipsychotics had been used for patients who refuse oral medications in delirium practice. The objectives were to investigate acceptability of transdermal antipsychotic patches by patients who refuse oral medications and their effectiveness in preventing recurrence of delirium. In this retrospective observational study, data were collected between October 2019 and December 2021. The sample was represented by patients hospitalized because of acute diseases or elective surgery who had delirium on the night before the consultation and had refused oral therapy after consultation. Delirium has been diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Instead, a transdermal patch of blonanserin, a second-generation antipsychotic drug, was tried. The primary outcome was the rate of patients who accepted it. The secondary outcome was recurrence rates of delirium. As much as 95.1% of patients who refused oral medications (98/103 patients) accepted to receive the transdermal patch. Of these, 24 patients developed delirium again, whereas all five patients who refused it developed delirium again [24.5% (24/98) vs. 100% (5/5); \( P = 0.0014 \)]. The present findings suggest that transdermal antipsychotic patches are more likely to be accepted by patients who refuse oral medications. Prospective studies are needed. \textit{Int Clin Psychopharmacol} 38: 23–27 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Delirium represents an acute change in cognition with altered consciousness and impaired attention that fluctuates over time (American Psychiatric Association, 2013; European Delirium Association and American Delirium Society, 2014). Multiple studies have found older age to be an independent risk factor for delirium among hospitalized, medically ill older adult patients, with an increased delirium risk from 3% for those less than 65 years old to 36% for patients 75 years and older (Pendlebury et al., 2015; Pinho et al., 2016; Maldonado, 2018). With the increase in the aged population, further increases in delirium seem likely. Therefore, attention has been increasingly paid to delirium prevention. There is moderate-certainty evidence regarding the benefit of multicomponent nonpharmacological interventions in hospitalized adults (Burton et al., 2021). Regarding pharmacological interventions, our randomized clinical trials have shown effects of a melatonin receptor agonist and an orexin receptor antagonist on delirium prevention (Hatta et al., 2014; Hatta et al., 2015; Hatta et al., 2017). Recent meta-analyses support these findings (Xu et al., 2020; Khaing and Nair, 2021). Furthermore, our prospective real-world data showed preventive effects of these drugs on the recurrence of delirium (Hatta et al., 2020). However, these drugs are not usable for patients who refuse oral medications, as they have only an oral formulation. Refusal of oral medications is unmet need of older people with delirium, especially, with comorbid behavioral and psychological symptoms of dementia. In that case, a frequent measure has been an antipsychotic injection such as intravenous or intramuscular haloperidol, which has some benefits of prophylactic use (Wang et al., 2012). In a recent meta-analysis of the pharmacological prophylactic measures for postoperative delirium, dexmedetomidine, olanzapine, and risperidone have shown higher efficacy than other drugs (Liu et al., 2019). However, dexmedetomidine hydrochloride injection is only indicated for sedation of nonintubated patients before and/or during surgical and other procedures (prescribing information of dexmedetomidine hydrochloride injection). Risperidone is not available in any formulation other than oral and long-acting antipsychotic injection, making it inaccessible to patients who refuse medication.
Olanzapine can accommodate patients who refuse medication because of the availability of intramuscular formulations, but their coercive actions often disrupt the patient-provider relationship. Therefore, we have been looking for a noninjection method that does not involve coercion.

The Japanese Ministry of Health, Labour and Welfare approved a transdermal patch of antipsychotic drug, which is blonanserin, in September 2019 for the treatment of schizophrenia in adults (LONASEN Tapes package insert). The transdermal patch of blonanserin has been expected to enhance treatment adherence for long course of schizophrenia treatment. Moreover, we noticed that patients who refused oral medications unexpectedly and frequently accepted to receive the transdermal patch. So, we began to use this patch for not only acute schizophrenia patients but also patients who had the hyperactive subtype of delirium on the night before the consultation and refused to take medicine orally after the consultation.

The objectives were to investigate acceptability of transdermal antipsychotic patches by patients who refuse oral medications and their effectiveness in preventing recurrence of delirium.

**Methods**

**Study design**

This is a retrospective, observational study, and all study protocols were approved by the Research Ethics Committee, Faculty of Medicine, Juntendo University (reference number; E21-0257). All methods were carried out in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects. The approved protocol did not require informed consent from the patients, as the design was retrospective, and because the data remained anonymous and were analyzed in aggregate. Instead, we posted a notice in the hospital providing a verbal explanation about the patch and could reject the recommendation. All patients received multicomponent, nonpharmacologic delirium prevention interventions by nurses (Ogawa et al., 2019). When patients developed delirium again, an injection of haloperidol was used as needed.

**Setting**

This study was conducted by trained psychiatrists as consultation-liaison psychiatric services in a university general hospital located in Tokyo. The period of data collection was 27 months (from 1 October 2019 to 31 December 2021), and that of follow-up was 2 weeks.

**Participants**

Patients were hospitalized because of acute disease or elective surgery and had the hyperactive subtype of delirium on the night before the consultation. They were introduced into consultation-liaison psychiatric services by the physician/nurse in charge and were assessed by two trained psychiatrists (K.H. and C.U.). Then, psychiatrists recommended patients to take delirium-preventive sleeping pills such as a melatonin receptor agonist and orexin receptor antagonists (Hatta et al., 2014; Hatta et al., 2015; Hatta et al., 2017) for the following nights. Among them, eligible patients were those who refused such oral medications. Alternatively, psychiatrists recommended a transdermal patch of blonanserin. Patients received a verbal explanation about the patch and could reject the recommendation. All patients received multicomponent, nonpharmacologic delirium prevention interventions by nurses (Ogawa et al., 2019). When patients developed delirium again, an injection of haloperidol was used as needed.

**Variables and measurement**

The patients’ demographic and clinical characteristics, including age, sex, BMI, presence or absence of dementia/MCI, previous delirium, admission diagnosis, habitual use of alcohol, habitual use of benzodiazepine receptor agonists, opioids, corticosteroids, scores of Clinical Dementia Rating (Hughes et al., 1982), Charlson Comorbidity Index (Charlson et al., 1987), and Eastern Cooperative Oncology Group performance status (Falkson et al., 1980), the serum level of C-reactive protein at the beginning of treatment, the cause of delirium according to the Delirium Etiology Rating Checklist (Trzepacz et al., 2010), and adverse events, were collected from medical records. Scores of sleep–wake cycle disturbances according to item 1 of the Delirium Rating Scale- Revisited-98, from 0 (not present) to 3 (severe disruption), were collected from medical records at the beginning of treatment and after 2 weeks (Trzepacz, 1999; Kato et al., 2010).

The primary outcome was the rate of patients who accepted to receive the transdermal antipsychotic patch among patients who refused oral medications. The secondary outcome was the rate of patients who developed delirium again during the first 2 weeks among them, compared with the rate in patients who refused both oral and transdermal formulations. A transdermal patch of blonanserin 20 mg was given at 15:00 until patients came to accept oral medications. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria were used to diagnose delirium by trained psychiatrists (K.H. and C.U.) at the consultation and every morning round.

**Statistical analyses**

As there was no prior study about the effect of transdermal antipsychotic patches on delirium in patients who refused oral medications, we could not set a particular study size. Instead, we tried to collect consecutive cases of more than 100.

To examine whether the transdermal patch of blonanserin would help prevent recurrence of delirium in
patients with delirium on the night before consultation, we compared patients who received it with those who refused it. For patients who were discharged before the end of the 14-day observational period, data during hospitalization were utilized.

Data were collected on standardized forms, and statistical analyses were performed using SPSS (version 28-J; IBM Japan, Tokyo, Japan). Differences between categorical variables in the patients’ demographics and clinical characteristics were calculated using Fisher’s exact test. Differences between sequential variables were calculated using unpaired t-tests (with Welch’s correction if applicable). If data were not sampled from Gaussian distributions, a nonparametric test (Mann–Whitney test) was used. We planned to construct multivariate logistic regression models to control for risk factors in estimating independent associations between the effects of the transdermal patch of blonanserin and the outcome of delirium as an exploratory analysis. All statistical tests were two-tailed. Differences were considered statistically significant at \( P < 0.05 \).

**Results**

Among 1764 patients who were referred to our consultation-liaison psychiatry team during the study period, 948 patients were diagnosed with delirium defined by the DSM-5. Of these, 103 patients presented with a hyperactive subtype of delirium on the night before the consultation and refused oral medicines after the consultation: 98 patients (95.1%) accepted to receive the transdermal patch, whereas five patients refused it (Fig. 1). There were no significant differences in demographic characteristics between the groups (Table 1).

Patients who received the transdermal patch of blonanserin developed delirium again less frequently than those who refused it \([n/N = 24/98 (24.5\%) \text{ vs. } 5/5 (100\%); \text{odds ratio, } 0.030; 95\% \text{ confidence interval, } 0.0016–0.56; \text{ } \( P \text{ } = \text{ } 0.0014\)]\). We did not construct multivariate logistic regression models because the recurrence rate of delirium in patients who refused the transdermal patch was 100%, and because no significant differences were found in demographic characteristics between the groups. Patients who developed delirium again received haloperidol injections as needed. Adverse events were observed in two patients who received the transdermal patch of blonanserin (1.9%): one was sleepiness, and another was slight extrapyramidal symptoms.

**Discussion**

The present study found that a high percentage of patients with delirium on the night before the consultation accepted the transdermal antipsychotic patch despite their refusal of oral medication. The reasons for the acceptance of the transdermal patch by these rejective patients might have been as follows. Patches are visible unlike oral medication. So, patients can remove them when they fill with apprehension against the drugs. To our knowledge, there is no study of transdermal patches regarding refusal of oral medication. In an open-label multicenter study about long-term safety and efficacy of blonanserin transdermal patch, patients’ attitudes to the patch were reportedly positive with respect to continuing treatment, compared with taking tablets (Iwata *et al.*,...
Thus, transdermal patches might have advantages of adherence or a patient-friendly character.

Second, the present study has shown a significant difference in the incidence of recurrence of delirium between patients who received the transdermal patch of blonanserin and those who refused it. This suggests that the transdermal patch of blonanserin is effective in preventing recurrence of delirium. Because of the noninvasive character, the transdermal patch of blonanserin may be a treatment choice regarding prevention of recurrent delirium in patients who refuse oral medication prior to an antipsychotic injection.

Transdermal antipsychotics have the potential to enhance treatment adherence, so the US Food and Drug Administration approved transdermal asenapine in 2019 for the treatment of schizophrenia in adults (Musselman et al., 2021). Its possible place in real-world practice has been sought. The present findings showing the transdermal patch of blonanserin may be a treatment choice regarding prevention of recurrent delirium in patients who refuse oral medication prior to an antipsychotic injection.

A major limitation of this study is retrospective design. In conclusion, the present findings suggest that transdermal antipsychotic patches are more likely to be accepted by patients who refuse oral medications. Furthermore, the transdermal patch of blonanserin might be effective in preventing recurrence of delirium in patients who had delirium on the night before the consultation. As transdermal patches appear to be superior to involuntary injections in maintaining a positive relationship between the patient and the medical staff, they may be an effective tool in practice. Prospective studies are needed.

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Conflicts of interest
K.H. has received lecture honoraria for Dainippon-Sumitomo, Eisai, Janssen, Meiji Seika, MSD, and Otsuka within the past 3 years. C.U. has received lecture honoraria for Shionogi, Eisai, and MSD, and consultation fees for Ono and TONIX within the past 3 years. H.N. declares that he has no conflicts of interest.

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