

## Immediate Resolution of Non-Withdrawal Delirium Through Daridorexant: A Report of Two Cases

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## 1. Abstract

We report here two cases of older women, 84 and 97 years old, who were admitted to our department for conservative treatment after a fall. Both women developed delirium in the course of the inpatient stay. After administration of 50mg Daridorexant, delirium was completely dissolved the next morning. Delirium did not recur even after discontinuation of medication. To the best of our knowledge, this is the first report of the efficacy of Daridorexant in the treatment of delirium. As part of an ongoing study in our department, these observations will be further objectified.

## 2. Introduction

Older patients endorse an increased risk for the development of delirium. Delirium has severe clinical and functional consequences. Therefore, the identification of patients at risk and multimodal non-pharmacological measures is the evidence-based management of delirium [1]. However, there is no reliable evidence of pharmacological prevention or treatment for delirium [2]. But adverse drug reactions occur significantly more frequent after application of antipsychotics to individuals with delirium [2].

In an ongoing study conducted in our department we investigate the incidence of delirium. In this study we collect personal and medical data, frailty, cognitive function, polypharmacy and anticholinergic burden of drugs.

Risk for delirium is assessed by the delirium risk assessment tool (DRAT), the incidence and the course of delirium is assessed by the 4 A-test. Non-pharmacological measures to prevent delirium belong to the clinical routine of the department. Preliminary data of this study show that the incidence of delirium is about 12% in individuals of 70 years and older despite application of team based non-pharmacological measures.

Recent case reports show, that suvorexant - an orexin antagonist approved in the US - was successful both as a prevention measure and as treatment for delirium as well [3]. Here we report on two cases with delirium we treated with daridorexant – an orexin antagonist approved in Germany for treatment of insomnia.

## 3. Case 1

A 84 year old woman presented with low back pain due to a vertebral fracture after she fell in her home. Geriatric assessment revealed impaired hearing and mild frailty (CFS 5). She had arterial hypertension and atrial fibrillation. Laboratory values were without abnormality. Exsiccosis was absent on admission. Delirium risk was moderate due to a DART score of 4 (impaired hearing, age). Her anticholinergic burden due to drugs was also moderate (ACB-score 2). Pain was controlled by mild opioids. On the afternoon at the admission day she became increasingly restless, disoriented and restless at night. Screening for delirium was positive

(4A-test 8). We started on 50mg daridorexant at the next evening. The next day, she presented calmer, was oriented and able to sleep at night. Repetition of 4A-test (2) showed resolution of delirium. Daridorexant was stopped at day three without rebound or recurring of delirium.

#### 4. Case 2

A 97 years old woman who lived alone at home was admitted to the emergency room after she was found lying on the floor for several hours by nurses. She presented with moderate frailty (CFS 5), mild exsiccosis. Her ACB was 2. On admission she was oriented and had no signs of delirium. The DRAT score was 4 indicative for a moderately elevated risk of delirium.

Cranial computed tomography showed a small subdural hematoma and no evidence of brain atrophy. Upon administration to our ward, she presented disoriented, sleepless and agitated. Non-pharmacological measures were initiated immediately, but delirium persisted. On day 3 we applied 50 mg Daridorexant in the evening. The next morning delirium was completely dissolved (NuDESC 1, CAM 0 and 4A-test 0). Daridorexant was stopped on day 7 without rebound or recurrence.

#### 5. Discussion

The management of delirium encompasses risk reduction, early diagnosis and non-pharmacological and pharmacological measures [4].

While the treatment of delirium traditionally centered around symptom management, there is a growing recognition that a multi-modal approach encompassing prevention, early detection, and targeted interventions is essential for optimizing patient outcomes.

Identifying patients at the highest risk of developing delirium is a necessary first step, risk reduction technique by the non-pharmacological techniques and early diagnosis is a critical issue. All these measures belong to our clinical routine.

Despite its prevalence and potential for severe consequences [5; 6], treatment of delirium has long been challenged by limited empirical evidence, resulting in a lack of standardized therapeutic strategies [7].

However, recently the evidence is growing that orexin antagonists might be effective in treatment for delirium. Some case reports present encouraging data about patient's response of delirium with suvorexant. The drug belongs to the orexin antagonist family with the indication insomnia [8].

Suvorexant was also effectively applied in the prevention of delirium [3] and also was effective in the prevention of delirium in an intensive care patient in a retrospective analysis [9] and in individuals in an emergency room as well [10]. In a study with treatment for delirium conducted in an ICU setting, orexin antagonist were more effective compared to antipsychotics [11].

Orexin stimulates different neurotransmitters which are linked to activation of the central nervous system including acetylcholine, histamine, noradrenaline, and dopamine. Therefore, orexins may be important in the etiology of stress-related psychiatric disorders like delirium [12].

Daridorexant is a novel dual orexin receptor antagonist, which was released for use in Europe in 2022. In Japan and the United States, two different substances of this category (suvorexant and Lemborexant) have been released in 2014 already and demonstrated potent effectiveness in sleep regulation [13]. Recently, the effect of suvorexant on nocturnal delirium was demonstrated [14]. To the best of our knowledge there is no sufficient data on the effectiveness of daridorexant on delirium in elderly patients. These case reports demonstrate that elderly patients with delirium in a hospital setting can benefit from daridorexant regarding sleep regulation and delirium. Further studies are warranted to confirm these preliminary findings. Furthermore, the preventive effect of daridorexant on patients at risk of developing delirium is another aspect worth to be investigated in future studies.

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