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## Effectiveness of Clonidine in Treating Dexmedetomidine Withdrawal in a Patient with Co-Existing Psychiatric Illness: A Case Report

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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**Conflict of interest:** None declared

**Patient:** Female, 40  
**Final Diagnosis:** Dexmedetomidine withdrawal  
**Symptoms:** Severe agitation • sweating • tachycardia  
**Medication:** —  
**Clinical Procedure:** None  
**Specialty:** Critical Care Medicine

**Objective:** Unusual or unexpected effect of treatment

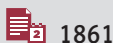
**Background:** Dexmedetomidine is a sedating agent approved for use in non-intubated patients and procedural sedation due to its efficacy in conscious sedation and minimal risks of respiratory depression. Previous reports proved the effectiveness of clonidine in treatment of withdrawal symptoms, but none have discussed cases with co-existing non-controlled psychiatric illness and prolonged duration of dexmedetomidine exposure.

**Case Report:** We report a case of a 40-year-old woman diagnosed with viral meningitis. Due to her complicated psychiatric illness and viral meningitis, she developed severe agitation unresponsive to standard therapy. The patient had to be placed on dexmedetomidine, to which she developed dependence. There were several attempts to gradually withdraw dexmedetomidine but these were unsuccessful despite adding multiple antipsychotic medications. Withdrawal was manifested in multiple symptoms, including severe agitation, sweating, and tachycardia. Clonidine was used and was an effective treatment option to successfully withdraw the patient from dexmedetomidine. A smaller initial dose was used due to low baseline systolic blood pressure, which was successful.

**Conclusions:** This report proves that clonidine is an effective option for treatment of dexmedetomidine dependence compared to other antipsychotic agents. The present report is the first to discuss severe psychiatric illness and prolonged dexmedetomidine duration (>7 days) in a non-intubated patient. Dexmedetomidine withdrawal must be considered in the differential diagnosis of patients with psychiatric illness, which can be easily treated with clonidine.

**MeSH Keywords:** Clonidine • Critical Care • Dexmedetomidine

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/908566>



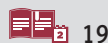
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## Background

Dexmedetomidine is a selective alpha-2 ( $\alpha$ -2) receptor agonist. It has been approved by the Food and Drug Administration (FDA) as a sedating agent for mechanically ventilated patients and for sedating non-intubated patients for surgical and other procedures [1]. Dexmedetomidine has minimal risk of respiratory depression and is successful in achieving conscious sedation in Intensive Care Unit (ICU) patients, which allows patients to be more awake and interactive [2,3]. Several studies have shown that dexmedetomidine infusions can be used safely for up to 28 days [4–7].

In pediatric and adult populations, it was observed that prolonged infusion of dexmedetomidine can cause dependence [8]. Clonidine has been suggested as a suitable option for treatment of withdrawal symptoms [8].

Clonidine is a centrally acting  $\alpha$ -2 receptor agonist that is structurally and functionally similar to dexmedetomidine [9–11]. Clonidine has sedative, anxiolytic, and analgesic properties [9,12] and thus has been used to treat anxiety and opiate and alcohol withdrawal, to improve mask application with the initiation of anesthesia and for pediatric procedural sedation [9,13–15]. Comparatively, clonidine's receptor affinity is predicted to be 200: 1 for  $\alpha$ 2 versus alpha-1 ( $\alpha$ -1) receptors, which is less than dexmedetomidine at 1600: 1 for  $\alpha$ 2 [10]. On the other hand, clonidine has the advantage of being able to be administered orally with excellent bioavailability and a longer duration of action.

Given the similar structural composition, there is emerging evidence for the use of clonidine to treat dexmedetomidine dependence and withdrawal [10]. A study in children showed that clonidine significantly decreased the duration of dexmedetomidine therapy [10]. Use of clonidine showed positive results in 2 adult patients [15], but the dose regimen is not clear.

The objective of this case report is to show that clonidine is an effective agent for the treatment of dexmedetomidine withdrawal using 0.1 mg as an initial dose, which contradicts previous conclusions from other publications.

## Case Report

We report a case of a 40-year-old woman brought to the Emergency Department by her husband in acute confusion state that started 2 days prior to admission.

**Demographics:** The patient weighed 53.5 kg. She was a housewife, married, with 2 children.

**Pre-hospital course:** The patient was in her usual state of health until 5 days before admission, when she started complaining of fever, headache, and dry cough. She was seen in a private clinic and was given acetaminophen. Two days later, she developed suppressed appetite. Later in the day, she developed behavioral changes and insomnia. One day later, her agitation was accompanied with irrelevant speech, so she was brought to the Emergency Department by her husband and admitted to the ICU.

The patient had a past medical history of anxiety and major depressive disorder. Her actual diagnosis was unclear to her and her family. Psychiatrists consulted on the case added antidepressants and antipsychotics but recommended that an in-depth psychiatric analysis be carried out as an outpatient. The patient was maintained on several home medications, including alprazolam, clonazepam, escitalopram, and fluoxetine, but the dosing regimen, duration, and compliance were not clear. Therefore, a psychiatry consultation was requested.

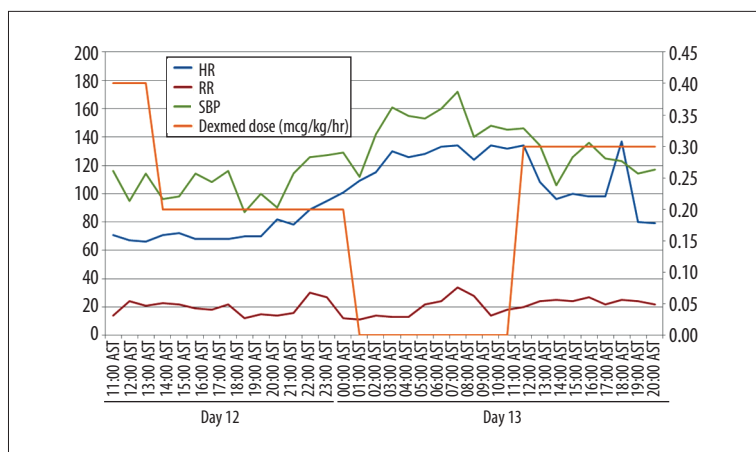
The patient had no relevant past surgical or family history. The family denied history of smoking, alcohol or drug abuse. She also had no history of any previous hospital admission or suicidal attempts. There was no history of food or medication allergy.

On clinical examination, the patient was conscious, disoriented, and restless. She was afebrile with positive neck rigidity. There was no skin rash, pallor, or jaundice. The rest of her systemic examination was unremarkable. She was hemodynamically stable and maintained good oxygen saturation on room air. Her initial vital signs were: respiration rate 18, blood pressure 127/93 mmHg, heart rate 90 bpm, and temperature 36.5°C.

With regards to her medical history and clinical examination, meningitis was at the top of the differential diagnosis list. Results of an urgent head computed tomography (CT) scan were normal and lumbar puncture (LP) was done after checking the coagulation profile and a cerebrospinal fluid (CSF) sample was sent to the lab.

**Hospital course:** On admission, the patient was conscious but disoriented and agitated. She received midazolam and fentanyl for LP procedure sedation. The patient was immediately given 8 mg IV dexamethasone STAT followed by initiating empiric antimicrobial and antiviral therapy that included acyclovir 10 mg/kg/dose q 8 h, Ceftriaxone 2 g twice daily, Vancomycin 1 g twice daily, and dexamethasone 4 mg IV q 6 h for 4 days as a part of standard meningitis therapy.

The patient's CSF results showed elevated protein (1.03 g/L) and elevated white blood cell count at 228/microL, mainly lymphocytic (89%) and a negative culture. The rest of her



**Figure 1.** Changes in systolic blood pressure, heart rate, and respiratory rate in response to the first trial of dexmedetomidine tapering.

initial laboratory results were within normal limits. As a result, the antimicrobial therapy was de-escalated to acyclovir and ceftriaxone.

The patient had altered speech, abnormal behavior, and agitation, which were thought to be manifestations of viral meningoencephalitis. During this period, the patient required a cumulative dose of 10 mg of midazolam. On day 2, the patient became restless and agitated and since she was not intubated, dexmedetomidine was initiated and titrated up to control agitation. The dose reached 1 mcg/kg/h. Additionally, midazolam was used on an as-needed basis to control breakthrough agitation.

Consequently, the patient was started on lorazepam 1 mg twice daily on regular basis on day 5. As the abnormal neurological condition continued on day 6, the team attempted to analyze the differential diagnosis for such symptoms. Therefore, the patient was scheduled for Magnetic Resonance Imaging (MRI) of the brain and LP was repeated to rule out tuberculosis meningitis or other etiologies. Both investigations were negative.

On day 6, the team decided to taper the dose of dexmedetomidine. This was successful until the dose reached 0.6 mcg/kg/hr on the next day. The weaning attempt failed on day 8 as the patient had episodes of severe restlessness, tachycardia, and tachypnea, which are classic withdrawal symptoms. Therefore, the dose was increased to 1.4 mcg/kg/h in addition to doses of lorazepam and midazolam as needed.

On day 9, the patient developed ICU delirium with potential for self-harm. Non-pharmacological measures for ICU delirium were started, which included visits by family and friends, watching television, and encouraging proper nighttime sleep. A psychiatrist was consulted, who started olanzapine 5 mg and clonazepam 1 mg once daily at bedtime in addition to haloperidol as needed. At this stage, the attempt to withdraw dexmedetomidine failed, as shown in Figure 1.

The patient showed slight improvement; therefore, another attempt to taper dexmedetomidine was made, but the patient had severe withdrawal symptoms of agitation, tachycardia, hypertension, and tachypnea. At this stage, the dose could not be decreased below 0.2 mcg/kg/h.

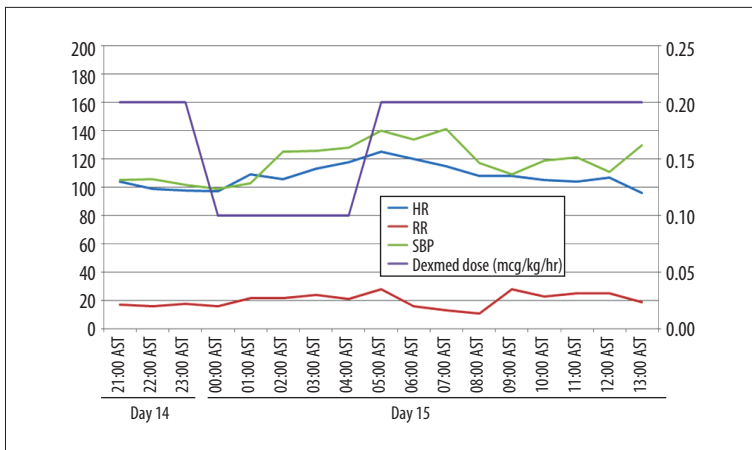
Despite resuming her home medications and adding olanzapine, there was a final attempt to withdraw dexmedetomidine on day 15, in which it was tapered down to 0.1 mcg/kg/h. However, the patient developed withdrawal symptoms, which again included elevated systolic blood pressure, tachycardia, and tachypnea, (Figure 2). Hence, the team decided to start the patient on clonidine. On day 16, enteral clonidine was initiated at a dose of 100 mcg every 6 h in an attempt to taper dexmedetomidine.

On day 18, the patient was calmer and more communicative, so gradual tapering of dexmedetomidine was re-started on the next day and dexmedetomidine was successfully stopped without agitation episodes on day 20, as shown in Figure 3.

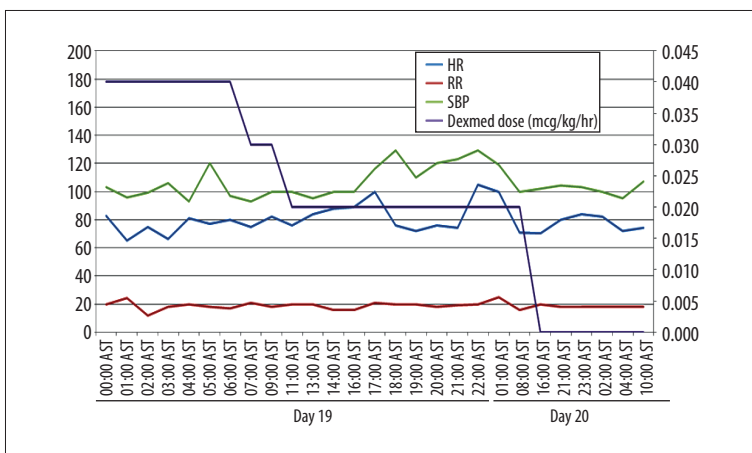
The prescribed clonidine regimen was 100 mcg every 6 h enterally for 4 days, then 50 mcg every 6 h for another 4 days, and then 25 mcg every 6 h for 4 days. Higher initial doses were not possible due to the sustained low baseline systolic blood pressure.

The patient had stable vital signs and was calm. The patient and her family were educated about the planned clonidine tapering regimen, as it would continue after discharge.

The patient was then shifted to the medical floor and discharged on the second day with a referral to a psychiatry hospital. A follow-up call was made several weeks later and the patient stated that she had stopped clonidine successfully with no episodes of agitation but stated that her depression status was not well controlled, but she is being followed up in a psychiatry clinic.



**Figure 2.** Changes in systolic blood pressure, heart rate, and respiratory rate in response to the second trial of dexmedetomidine tapering despite adding olanzapine.



**Figure 3.** Changes in systolic blood pressure, heart rate, and respiratory rate in response to the dexmedetomidine tapering after adding clonidine.

## Discussion

PubMed and Medline databases were searched to determine the current literature that evaluated dexmedetomidine withdrawal and the treatment strategies to manage it. The keywords (dexmedetomidine, withdrawal, and clonidine) were used during the search. The results were filtered to show human studies and a few observational studies. A total of 33 results were found. A few studies were found to be relative, some of which discussed pediatric cases.

The present case is unique because viral meningitis can be associated with neurological manifestation. In addition, this patient had a psychiatric illness of a special nature and she was unable to be successfully treated with different antipsychotic or antidepressant agents. There are no published studies to date providing in-depth discussion of the combination of severe psychiatric illness and prolonged duration of dexmedetomidine in non-intubated patients. Important key factors in determining dexmedetomidine withdrawal are tachycardia, tachypnea, and increased blood pressure [18]. This case report provides more in-depth information and slightly different conclusions than discussed in previous publications. The aspects are discussed below:

There are different dosing regimens suggested in the literature. One of the cases received 0.1 mg twice daily and tapered over 4 days [15]. For alcohol withdrawal, the following dosing regimen was suggested: 0.15–0.3mg every 6 h [14]. An observational study recommended that an initial dose of 0.2–0.3mg was preferred to 0.1 mg during the transition from dexmedetomidine to clonidine in ICU patients and re-initiating clonidine in case of any withdrawal symptoms [17]. However, this patient had a low average baseline systolic blood pressure of 100 mmHg, so higher doses were not possible. Therefore, a lower initial dose can be successfully used with no hypotension. The case was followed up 4 weeks after discharge, but no other studies reported similar observations.

This is the first case to discuss a withdrawal protocol in adults with prolonged dexmedetomidine duration that lasted longer than 7 days in non-intubated patients vs. other case reports [19]. This consequently led to a longer duration to discontinue dexmedetomidine, 48 h vs. 8 h [19] and a longer duration of clonidine therapy, 12 days vs. 4–6 days [15].

The patient had psychiatric background on therapy and any sort of agitation is, sometimes, uncontrollable and can lead

to severe emotional lability and hemodynamic instability. This can mask the possibility of dexmedetomidine withdrawal. For this patient, dexmedetomidine withdrawal symptoms were unresponsive to the benzodiazepines or any of the antipsychotic medications administered as mentioned above. Other studies failed to compare clonidine to other antipsychotic agents [19].

Therefore, the present case report provides a clear dose regimen, which was proven to be successful in tapering of low-dose dexmedetomidine without hypotension or other adverse effects.

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## Conclusions

Dexmedetomidine withdrawal must be considered in patients with psychiatric illness in the ICU. Clonidine is an effective treatment option for dexmedetomidine withdrawal. Given the prolonged duration of the sedative agent, clonidine may be initiated at lower doses (0.1 mg), which can be safely used in patients with lower systolic blood pressure.

## Conflict of interest

None.