Benzodiazepine Maintenance Treatment in Schizophrenia

To the Editor: Data are conflicting concerning the utility of benzodiazepines in management of schizophrenia with comorbid substance use. We present 2 cases that offer different rationale for benzodiazepine maintenance therapy.

Case reports. Ms A is a 54-year-old woman with schizophrenia (*DSM-5*[1]) and a 17-year history of benzodiazepine and opioid use. Prior to her initial hospitalization, Ms A was on a prescribed 4-year regimen of 30 mg of diazepam. During this time, she experienced chronic delusions and hallucinations but was stable enough that she did not require antipsychotic treatment or hospitalization. After taper of diazepam, the patient underwent several psychiatric hospitalizations for psychotic decompensation. During her most recent hospitalization, Ms A was started on haloperidol decanoate; however, she did not improve sufficiently for discharge on haloperidol alone. Low-dose benzodiazepines were resumed (clonazepam), and Ms A's psychosis improved sufficiently to facilitate discharge, but did not remit fully.

Mr B is a 29-year-old man with schizophrenia (*DSM-5*[1]) complicated by tardive dyskinesia, plus remote history of LSD (lysergic acid diethylamide) and cocaine use disorders (*DSM-5*[1]). He was admitted to the psychiatric unit within the hospital for clozapine initiation and lorazepam taper. He had been started on lorazepam 1.5 mg/d for catatonia 4 years prior to admission. During these years, while concurrently taking risperidone 3 mg twice daily, Mr B's lorazepam dose was increased to 10 mg/d. He remained consistent in his belief that only lorazepam alleviated his paranoia and somatic delusions. On a therapeutic clozapine dose, Mr B's psychotic symptoms improved, but he remained unwilling to taper lorazepam.

The use of benzodiazepines as monotherapy or as an adjunct to antipsychotics in schizophrenia has been assessed with conflicting results.[2–4] Dold et al[2] reviewed 34 randomized controlled trials evaluating benzodiazepine treatment in schizophrenia. The reviewers reported no conclusive evidence supporting use of benzodiazepines alone or in combination with other medications.[2] In contrast, other studies[3,4] reported that short-term monotherapy treatment with benzodiazepines decreased positive and negative symptoms in one-third to one-half of patients; these studies demonstrated efficacy of benzodiazepines as antipsychotic treatment adjuncts.

Literature reporting γ-aminobutyric acid (GABA) dysfunction in schizophrenia suggests a role for benzodiazepine pharmacotherapy.[5] In schizophrenia, cortical GABAergic neurotransmission appears to be down-regulated, leading to changes associated with impaired somatosensory information processing.[5] Likely as a compensatory mechanism for excitatory desynchronization, up-regulation of high-affinity postsynaptic $GABA_A$ receptors occurs, independent of antipsychotic treatment duration.[5] By targeting $GABA_A$ receptors, benzodiazepines might normalize GABAergic transmission, allowing for a novel mechanism of treatment for psychosis.[5] This hypothesis is supported by the case of Ms A, who did not require antipsychotic medication until her 50s. Although not definitive treatment for schizophrenia, benzodiazepines may have facilitated sufficient health for Ms A to remain in the community with relatively high quality of life for a long period of time. Once hospitalized, Ms A did not recover sufficiently for discharge without benzodiazepines, which may have been due to direct treatment effect, although it cannot be definitively proven.

The evidence supporting benzodiazepine use in schizophrenia is challenged by the risks of prescribing a highly abused substance to a vulnerable population.[6] In a prospective analysis[6] of benzodiazepine use in patients with bipolar disorder or schizophrenia and comorbid substance abuse, patients prescribed benzodiazepines were more likely to have abused benzodiazepines during the study compared to those not prescribed benzodiazepines. While exposure does appear to play a role in this abuse profile, patients taking prescribed benzodiazepines displayed increased illness severity at presentation.[6] It remains unclear whether benzodiazepine access alone increases risk of misuse.[7]

Current treatment for benzodiazepine use disorder focuses on controlled withdrawal, followed by abstinence.[8] However, in patients who develop a use disorder secondary to long-term benzodiazepine treatment for psychiatric indications, abstinence may not be a feasible goal. In Mr B's case, although the benzodiazepines were initially indicated for catatonia, he developed an overvalued belief in their role in his treatment. Abstinence became unachievable, although dose reduction occurred. Therefore, in the cases described here, long-term use of benzodiazepines either was useful in clinical improvement (Ms A) or became intricately tied to delusions and belief in one's own improvement (Mr B), making abstinence impractical.

With the infeasibility of abstinence for patients such as Mr B, agonist substitution might be an alternative.[8] Using this model, maintenance treatment with a long-acting, slow-onset benzodiazepine would be analogous to methadone maintenance for opiate use.[8] By using a benzodiazepine and maintaining stable blood benzodiazepine levels, patients would be less likely to experience sedation, withdrawal complications, and craving.[8] Agonist substitution could facilitate treatment retention in an unstable patient population, rather than "doctor shopping" for benzodiazepine prescriptions during withdrawal.[8]

Given evidence supporting a GABAergic mechanism for schizophrenia, treatment with benzodiazepines may target a novel therapeutic mechanism beyond the scope of traditional antipsychotics. In patients using benzodiazepines for relief of psychotic symptoms, we present a role for maintenance therapy using agonist substitution.

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