Catatonia and Its Treatment

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Psychiatric diagnoses are currently categorized on a syndromic basis. The syndrome of catatonia, however, remains in a diagnostic limbo, acknowledged predominantly as a subtype of schizophrenia. Yet, catatonia is present in about 10% of acutely ill psychiatry patients, only a minority of whom have schizophrenia. Among those with comorbid affective disorders, who comprise the largest subgroup of catatonic patients, the catatonic signs typically resolve dramatically and completely with benzodiazepine therapy. Those with schizophrenia respond less reliably, suggesting that the underlying processes causing the catatonia may be different in this group. The majority of patients with catatonia have concurrent psychosis. Failure to treat the catatonia before institution of antipsychotic medication may increase the risk of inducing neuroleptic malignant syndrome. At this point of time, the pathobiology of catatonia is unknown; the major reason for considering catatonia as a separate diagnostic entity would be to increase recognition of this eminently treatable neuropsychiatric syndrome.

Key words: catatonia/treatment/benzodiazepines

One of the most dramatic of clinical phenomena is the response of catatonia to treatment with benzodiazepines (BZPs).[1–4] Within 3 hours of receiving lorazepam 1–3 mg sublingually or intramuscularly, the vast majority of catatonic patients, who have been immobile, mute, withdrawn, and refusing to eat or drink, enjoy complete release from their "frozen" state. This situation is remarkably akin to the "awakenings," described by those who first treated parkinsonian patients with levodopa.[5] As Fink et al[6] emphasize in their article, the availability of a safe, convenient, and highly efficacious treatment demands a rethinking of the "place" or status of catatonia in our current diagnostic system.

Because an estimated 9%–15% of patients admitted to a typical acute care psychiatric service meet diagnostic criteria for catatonia,[2,7,8] it is of obvious interest to know whether all catatonic patients respond equally to BZPs. We have had the opportunity to address this issue in 180 episodes of catatonia in 148 individuals (78 men and 70 women; mean age = 44 y, range = 14–89 y) studied in our acute care service over the past 20 years. The diagnosis of catatonia was made according to previously published criteria[2] that include 12 different clinical features, based upon the original description of this condition by Kahlbaum et al[9]. Similar to those described in Kahlbaum et al's monograph, our patients have had a predominantly retarded type of catatonia. Almost every patient displayed the combination of immobility, mutism, and withdrawal; negativism, posturing, grimacing, and rigidity were present in 55%–65%, whereas the more unusual features of waxy flexibility, stereotypy, echolalia, echopraxia, and episodic verbigeration were seen in less than 35% of cases.[10] The distribution of concurrent or underlying diagnoses in these catatonic patients has been as follows: affective disorder (AD): 46%, schizophrenia: 20%, schizoaffective (SA) disorder: 6%, a range of medical/neurological illnesses: 16%,[10] BZP withdrawal: 4%,[11] and other psychiatric disorders: 8%. As we have followed almost all these patients in our clinic over the past 20 years, we are confident of these diagnoses. The range of clinical settings in which catatonia has developed would support the proposal of Fink et al[6] that catatonia be divorced from its present association with schizophrenia.

In our series, we have found a differential response to BZP therapy among the various diagnostic subgroups. Response is defined as a complete resolution of all catatonic signs. The more unusual features, such as waxy flexibility, clear and patients begin to talk, eat, move about, and cooperate with an assessment. For the vast majority of patients, this occurs within 3 hours of the first dose of lorazepam or within 3 hours of a second dose. More than 80% of those with AD enjoyed a prompt and robust resolution of catatonic signs after introduction of the medication, as did 70% of the patients with SA disorder. By contrast, those with a diagnosis of schizophrenia did not fare nearly as well,[2,10]

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a result consistent with an earlier report by Ungvari et al.[12]

We have considered a number of reasons why catatonic patients with a primary diagnosis of schizophrenia may not respond as reliably or robustly to BZPs.

1. Differential duration of the catatonic syndrome prior to treatment: Examination of our data suggests that duration of the catatonic syndrome is not, in itself, a critical factor in determining the response to BZPs. Prior to treatment, all patients with an episode duration of <30 days had been in a catatonic state for at least 24 hours, with an average duration of 6.7 days for those with AD and 7.1 days for those with schizophrenia. In a subgroup of 12 patients, with catatonia of greater than 30-day duration prior to treatment, there were equal numbers of those with AD ($n = 4$), schizophrenia ($n = 4$), and atypical psychosis ($n = 4$). A full or complete response was observed in 75%, 50%, and 100%, respectively, in each diagnostic group. Importantly, while the response in those with a longer duration of catatonia may be complete, it may also be slower and resolve over a matter of months rather than days.[13,14]

2. Different pathobiologies: The differential treatment response of catatonia to BZPs suggests that the underlying biology of the syndrome may be different in patients with schizophrenia than in those with mood disorders. This may relate to the degree to which catatonia is a more integral and enduring aspect of schizophrenia and to why some studies have found a unique profile of catatonic signs in those with schizophrenia vs AD. For example, Ungvari et al[15] note the higher frequency of features such as bizarre posturing, automatic movements, and stereotypies as opposed to immobility, mutism, and withdrawal in those with chronic schizophrenia.

3. Differences in the nature and severity of psychosis among patients with catatonia: In our series, upward of 75% of catatonic patients, across diagnostic groups, reported having psychotic symptoms during the episode, and this feature itself did not appear to influence the robustness of the response to BZPs. We did not, however, capture the severity and/or nature of the psychotic symptomatology or the relative burden of positive vs negative symptoms for those with AD compared with those with schizophrenia. We think that such information would contribute to our understanding of the noncatatonic clinical features that influence the response to BZP medication.

4. Differences in the predominant affective state of patients in each group during the catatonic episode: Fink et al[6] refer to Jaspers' description of catatonic patients as being "capable of no reaction, of no affective display and of no action." Retarded catatonia has also been likened to a state of petrification or being "scared stiff."[16,17] Given that BZPs are anxiolytic agents, we have considered whether patients who recall having been in a state of intense fear, when catatonic, might be the most likely to respond to treatment. Our practice has been to inquire about this in all patients, as soon as possible after the catatonia resolves. We have found that more than 60% of those with AD, but only 30% of those with schizophrenia, endorse having been in a state of fright. In most cases, fear appeared to have preceded the immobility although several patients have reported being afraid because they were unable to move.

If, then, the majority of patients with catatonia are psychotic, and if catatonia, in those with core psychotic illnesses such as schizophrenia, responds less well to BZPs, how should one approach treatment? This is a highly relevant issue given that catatonia might be a risk factor for the development of neuroleptic malignant syndrome (NMS), an observation reported by Weinberger and Kelly[18] as early 1977. White and Robbins[19] described 5 patients with excited catatonia—characterized more by frenzied activity than immobility—who went on to develop NMS after being treated with antipsychotic drugs (APDs), and Lee[20] confirmed this finding, proposing that low serum iron might be a marker for those at risk of developing NMS when exposed to APDs. Most recently, Paparrigopoulos et al[21] reviewed this issue in the context of reporting a catatonic patient who developed NMS after treatment with clozapine. At the present time, however, there is no information available regarding the proportion of catatonia case subjects who might go on to develop NMS when treated with APDs. Our extensive experience with both catatonia and NMS[22,23] may shed some light on this issue. Of the 180 catatonic episodes we have studied, 82 patients received APDs, at some point, while catatonic. In 3 instances (3.6%), NMS developed. This rate is significantly higher than the currently estimated incidence of 0.07%–1.8% in all APD-treated patients.[24] Looking at this from another perspective, we have assessed and treated 56 cases of NMS over the past 25 years and have carried out careful chart reviews to determine the psychomotor status of the patients at the time they received the APD that resulted in the NMS episode. In 15 instances (27%), retarded catatonia was specifically documented. Given the inevitable deficiencies in documentation and the underrecognition of catatonia as a clinical syndrome, it is likely that this is an underestimation of how frequently catatonia and NMS are temporally linked. Taken together, our finding that hypoferremia (an indicator of acute phase activation) is a consistent and reproducible finding in NMS[25], in conjunction with Lee's[20] observation that exposure to APDs is much more likely to induce NMS in catatonic patients with low serum iron, and our own data indicating that NMS is a manifestation of the acute phase response,[26]

we would propose that the prior activation of acute phase proteins might be the key feature that predicts which catatonic patients are at risk of developing NMS on exposure to APDs.

While we support a reclassification of catatonia that would lead to improved recognition and treatment of the syndrome, we are less enthusiastic about the proposal by Fink et al[6] to include NMS and serotonin syndrome as subtypes of catatonia. These toxidromes have distinctive autonomic and biochemical profiles and are typically associated with an encephalopathy as opposed to the clear consciousness of most patients with catatonia. Furthermore, the currently available evidence indicates that the critical interventions in both NMS and serotonin syndrome are withdrawal of the offending agents and timely supportive care. The main reason for rethinking the categorization of catatonia, in our opinion, is the availability of a safe and effective treatment in the form of BZP medication. While we agree with Ungvari et al[15] in this issue that there is a lack of conceptual clarity regarding the term catatonia, there is a consistent and compelling literature supporting the therapeutic efficacy of BZPs in the treatment of the clinical syndrome characterized by immobility, mutism, and withdrawal.

To summarize, (1) retarded catatonia is common in the acutely ill psychiatric population; (2) although no double-blind placebo-controlled trials have been carried out, it has been consistently observed to be highly responsive to BZP treatment; (3) the presence of catatonia may increase the risk of NMS if patients are exposed initially to APDs while still catatonic; and (4) catatonia can occur in a very wide range of illnesses, both medical and psychiatric. At a practice level, we recommend the following approach.

1. Always consider the diagnosis of catatonia, particularly when presented with an immobile, mute, often rigid patient who nonetheless typically appears alert and attentive or when confronted with a patient in an extreme state of excitement. One need not use specialized rating scales for catatonia, most of which are more appropriate to the research setting than to the bedside.
2. In suspected cases of catatonia, determine the current medication regimen, record vital signs regularly, and obtain appropriate blood work particularly complete blood count, hematocrit, electrolytes, blood urea nitrogen, creatinine, serum iron, and creatine phosphokinase. Arrange for brain imaging and electroencephalography to rule out nonconvulsive status epilepticus and encephalopathic conditions that can mimic catatonia.[10] Fortunately, in patients with predominantly retarded catatonia, these tests are relatively easy to carry out, whereas this is often impossible in those in a state of excitement.
3. Administer lorazepam 1–2 mg, alone, sublingually or intramuscularly. If this is ineffective, it should be repeated again in 3 hours and then again in another 3 hours. In our experience, this is an adequate trial for the majority of patients, who have had catatonia of the retarded type for less than 3 weeks. Lower initial and subsequent dosages may be necessary for elderly patients, and chronic catatonia may respond over days or months, rather than hours. The issue of whether some BZPs might work better than others has not been carefully studied.
4. The dosage of BZP medication that was effective in resolving the catatonia should be continued, until treatment of the primary disorder is well underway. This, of course, must be titrated against sedation. If BZPs are not maintained until treatment of the comorbid condition is underway, it is our experience that patients tend to relapse.
5. A course of electroconvulsive therapy (ECT) should be considered if the catatonia shows minimal or no response to BZP treatment. This is also the treatment of choice for those with lethal or malignant catatonia[27] as discussed in the article by Fink et al.[6] As a result of mutism and an inability to cooperate with an interview or examination, catatonic patients cannot make decisions about this treatment, and surrogate consent must be obtained.
6. Once the catatonia has resolved and patients are moving about normally and eating and drinking, APDs may be introduced without undue risk of precipitating NMS.
7. In the event that the catatonia does not resolve with either BZPs or ECT, or if surrogate consent for ECT cannot be obtained, and it is clear from the patient's prior documented history or information provided by the family that the underlying illness is a primary psychotic disorder, we suggest initiation of APDs while maintaining the patient on BZPs. We feel, at this point, that there is enough concern in the literature about the risk of NMS in catatonic patients to warrant discussion of this issue with those who are making treatment decisions.

While BZPs are extremely safe medications when used in the short term, several issues should be kept in mind during BZP treatment. They include (1) the risk of hypoventilation in obese patients or those with obstructive sleep apnea, (2) falls in elderly patients or those with balance problems after they start to move about following resolution of their catatonia, and (3) the potential, albeit small, for previously immobile patients to switch into a more excited form of catatonia. When the catatonic state is successfully treated and patients become more cooperative, physical and psychiatric examinations as well as additional investigations can be carried out if required. Expeditious treatment will typically obviate the need for interventions such as intravenous hydration and catheterization as patients begin to eat and drink almost immediately.

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