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154 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Catatonia Catatonia is a neuropsychiatric disorder that presents with a wide range of signs and symptoms, covering focal and generalised motor activity, speech, affect, complex behaviour and autonomic function.¹ A comprehensive meta-analysis of international data from 74 studies, conducted between 1935 and 2017 and involving 107,304 individuals, found an overall pooled, mean prevalence of catatonia of just over 9% in patients diagnosed with a range of psychiatric and medical conditions.² Three main catatonia subtypes are recognised: a retarded or stuporous form with decreased psychomotor behaviour; an excited form, characterised by agitation, combativeness, impulsivity and apparently purposeless overactivity; and malignant catatonia, a life-threatening state that presents as catatonia with clinically significant autonomic abnormalities, including raised blood pressure and body temperature, and change in heart rate and respiratory rate.^{1,3-5} The retarded form tends to present as stupor – the key features include mutism, rigidity, marked psychomotor retardation, negativism, posturing, waxy flexibility and catalepsy. While historically associated with schizophrenia, stupor is also seen in other psychiatric conditions such as depression and, less commonly, mania,⁶⁻¹¹ alcohol¹² or benzodiazepine withdrawal,¹³ and conversion disorder.^{6,7,14-20} If psychiatric stupor is left untreated, physical health complications are unavoidable and develop rapidly. Prompt treatment is crucial to prevent serious complications such as dehydration, venous thrombosis, pulmonary embolism, pneumonia and, ultimately, death.²¹ A catatonic syndrome is most commonly associated with psychiatric conditions such as bipolar disorder, schizophrenia and major depressive disorder,^{1,2} but may also be seen in patients with postpartum psychosis,²²⁻²⁴ post-traumatic stress disorder,^{25,26} developmental disorders such as autism spectrum disorder, neurodegenerative conditions,^{27,28} and a range of underlying medical conditions, including: ■ ■subarachnoid haemorrhages ■ ■basal ganglia disorders ■ ■non-convulsive status epilepticus ■ ■locked-in and akinetic mutism states ■ ■endocrine and metabolic disorders (e.g. Wilson's)²⁹ ■ ■Prader-Willi syndrome ■ ■antiphospholipid syndrome³⁰ ■ ■autoimmune encephalitis, such as anti-NMDAR encephalitis^{1,31-33} ■ ■systemic lupus erythematosus^{34,35} ■ ■infections (especially CNS infections) ■ ■dementia ■ ■drug withdrawal and toxic drug states (e.g. after abrupt withdrawal of clozapine and withdrawal of zolpidem, benzodiazepines³⁶ and many non-psychotropic medications, including medicines used in oncology). Treatment The treatment of stupor in the context of catatonia is somewhat dependent on its cause but should usually include benzodiazepines. Benzodiazepine monotherapy is the treatment of choice for stupor occurring in the context of affective and conversion

Schizophrenia and related psychoses CHAPTER 1 disorders.^{8,9,37} It is postulated that benzodiazepines may act by increasing gamma-aminobutyric acid (GABA)ergic transmission or

reducing levels of brain-derived neurotrophic factor.³⁸ There is most clinical experience with lorazepam.^{32,39} Many patients will respond to standard doses (up to 4mg/day) but repeated and higher doses (between 8 and 24mg per day) may be needed.⁴⁰ One small, observational study of patients with catatonic stupor in the context of a mood disorder⁸ (either major depressive disorder or bipolar I disorder) used a lorazepam-diazepam treatment protocol and reported a response in 10 of the 12 patients with intramuscular lorazepam 2–4mg. In another study, which followed a very similar protocol, relief of symptoms was achieved in 18 of 21 patients with catatonia caused by general medical conditions or substance misuse.⁴¹ Where benzodiazepines are effective, onset effect is rapid. A test dose of zolpidem (10mg) may predict response to benzodiazepines⁴² and frequent dosing of zolpidem may provide effective treatment.^{43,44} IV lorazepam has also been used to predict response.⁴⁵ Catatonia in schizophrenia may be somewhat less likely to respond to benzodiazepines alone, with a response in 40–50%⁴⁶ of cases. A double-blind, placebo-controlled, crossover trial with lorazepam up to 6mg/day demonstrated no effect on chronic catatonic symptoms in patients with established schizophrenia,⁴⁷ similar to the poor effect of lorazepam seen in a non-randomised trial.⁴⁸ A Cochrane review⁴⁹ searched for RCTs in which people with schizophrenia or other similar severe mental illness had received benzodiazepines or another relevant treatment for catatonia. Only one study was eligible, which involved 17 participants treated with lorazepam or oxazepam; there was no clear difference in effect. The authors noted that no data were available for benzodiazepines compared with either placebo or standard care. A further complication in schizophrenia is that of differential diagnosis, which includes EPSEs and the NMS. Debate continues regarding the similarities and differences between catatonic stupor in psychosis and NMS.^{50–53} Malignant catatonia⁵ may not be distinguishable from NMS, either clinically or by laboratory testing, which has prompted the view that NMS may be a variant form of malignant catatonia.⁵⁴ However, NMS can probably be ruled out in the absence of any prior or recent administration of a dopamine antagonist. The vast majority of evidence published recently and over previous decades suggests that prompt ECT remains the most successful treatment for catatonia.^{39,45,48,55–71} ECT-responsive catatonia has been recognised in the context of NMS, delirious mania, autism spectrum disorder and limbic encephalitis.^{53,72} While it has been suggested that response to ECT may be lower in patients with schizophrenia (or in those who have been treated with antipsychotic medication) than in patients with mood disorders,⁷³ ECT is still considered the treatment of choice for catatonic schizophrenia that has failed to respond to an adequate trial of benzodiazepines.^{1,74} In malignant catatonia, every effort should be made to maximise the effect of ECT by using liberal stimulus dosing to induce well-generalised seizures.⁷⁵ Physical health needs should be prioritised, with inpatient medical care being provided, when necessary, especially for those showing autonomic instability and those for whom dietary intake cannot be managed in psychiatric care. A 2024 systematic review⁷⁶ of studies of ‘non-invasive brain stimulation’ techniques for catatonia reinforced ECT as an effective treatment and suggested that it may be considered as first-line therapy in certain cases, but also identified rTMS and

156 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 tDCS as promising treatments, although high-quality RCTs are required to establish efficacy.^{76,77} The use of antipsychotic medication should be carefully considered. Some authors recommend that such treatment should be avoided altogether in patients with catatonia, although there are reports of successful treatment of catatonia with clozapine,⁷⁸ as well as other SGAs, such as olanzapine, aripiprazole, risperidone and ziprasidone,^{1,79–85} (particularly in cases of catatonic schizophrenia).⁸⁶ There are also case reports of combination treatment with antipsychotic and benzodiazepine medication proving

effective when each has failed individually.^{87,88} When considering the use of antipsychotic medication, account should be taken of the patient's history, their psychiatric diagnosis and previous response to antipsychotic treatment. If stupor develops in a patient on antipsychotic medication, any treatment with antipsychotic medication should be avoided if there are any signs or symptoms of NMS. Where NMS can be ruled out and stupor occurs in the context of non-adherence to antipsychotic treatment, early re-establishment of antipsychotic medication is recommended, with consideration of adjunctive benzodiazepines. This may be particularly relevant when catatonic symptoms have occurred following discontinuation of clozapine.^{36,89} Catatonia has also been reported after withdrawal of long-term benzodiazepine treatment.³⁶ When physical health conditions, as in the examples listed earlier this section, are associated with a catatonia-like clinical picture, treatment of the underlying medical condition (e.g. lupus)⁹⁰ is warranted. A treatment algorithm for catatonic stupor⁹¹ is provided in Figure 1.4. The 2023 British Association for Psychopharmacology consensus guideline for the management of catatonia¹ includes a more detailed referenced algorithm for the management of the condition. Medications other than benzodiazepines reported as treatments for catatonia/ stupor are listed in Table 1.34.

Schizophrenia and related psychoses CHAPTER 1 Stupor in the context of affective/conversion disorder Stupor in the context of psychotic illness NMS possible No response after 1-2 days Not taking antipsychotic medication No response after 1-2 days No response after 1-2 days Exclude or treat underlying physical illness Lorazepam up to 4mg/day* Start with 2mg and give a further 2mg if no effects after 3 hours Use IM route subsequently Rule out NMS Lorazepam** high dose 8-24mg/day ECT† Consider SGA‡ e.g. clozapine, olanzapine Some authorities recommend co-therapy with benzodiazepines Follow benzodiazepine/ECT protocol opposite NMS ruled out *Lorazepam is absorbed sublingually and is tasteless. This route may be preferred in non-cooperative patients or those who cannot swallow. **Intravenous diazepam or lorazepam may be considered here. †Do not wait to give ECT if there is significant danger to life. ‡There is considerable uncertainty about the use of antipsychotic medication for catatonic stupor. Antipsychotics can induce catatonia⁹² and risk of NMS in catatonic schizophrenia is much higher than with non-catatonic schizophrenia.⁹³ An alternative approach is to use antipsychotic medication either once catatonia has resolved or when benzodiazepines or ECT have failed and there is clear evidence of a psychotic illness.⁹¹ Figure 1.4 Algorithm for treating catatonic stupor.⁹¹

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