**Are Benzodiazepines Effective in Treating Catatonia?**

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**Keywords**: catatonia, benzodiazepine, lorazepam, oxazepam, schizophrenia, mental illness

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**Abstract**

Establishing an evidence base for the clinical management of catatonia is made difficult by the heterogeneous nature of the condition and the limited understanding of its pathophysiology. Benzodiazepines and electroconvulsive therapy are the mainstays of treatment. The Cochrane review discussed is an update of a previous so-called “empty review” into the use of benzodiazepines in treating catatonia compared to placebo, electroconvulsive therapy or other psychotropic medications. This identified only a single study with 17 participants with catatonia who received either lorazepam or oxazepam as benzodiazepine monotherapy. It showed no difference in the clinical change in symptoms between the groups as measured by a 50% improvement on the Visual Analogue Scale. There were no data for other measures of general function, adverse effects or hospital stay. Therefore, robust clinical conclusions on the treatment of catatonia could not be established and further studies are needed to assess the outcomes of benzodiazepine use in the treatment of catatonia. This commentary discusses the findings in more detail.

**Introduction**

Catatonia is a complex and heterogeneous psychomotor syndrome. Symptoms can be categorised into four groups including disturbances of motor function, volition, disinhibition and autonomic instability (Walther 2016, Walther 2012) [Table 1]. There are numerous organic (Box 1) and functional causes of catatonia including affective disorders, schizophrenia spectrum disorders, neurodevelopmental disorders, dementia and drug intoxication (Walther 2016). Without treatment, the mortality from catatonia is high (Healy 2012, Tuerlings 2010). The subtype of malignant catatonia is characterised by pyrexia, behavioural agitation, delirium and autonomic instability alongside the motor symptoms of catatonia. This is life-threatening condition where early diagnosis and treatment are crucial (Park 2017). Patients with catatonia are also an increased risk of malnutrition, dehydration, pneumonia and venous thromboembolism (Penland 2006, Regestein 1977). The underlying mechanism remains poorly understood. N-methyl-D-aspartate (NMDA) receptor hypofunction and dysfunction of the cortical and basal ganglia motor circuits have been implicated. We would direct readers to comprehensive review articles on this topic by Walther et al. (Walther 2016, Walther 2019) and Rogers et al. (Rogers 2019).

In clinical practice, benzodiazepines are the most commonly used treatment (Sienaert 2014, Fink 2013). High doses may be required for effective treatment (Fink 2009, Lin 2017). In life threatening or treatment-resistant cases, electroconvulsive therapy (ECT) is the treatment of choice. However, there are no widely accepted clinical guidelines for the treatment of catatonia. While numerous case reports and small studies are available, there is a paucity of higher quality research into both the pathophysiology and the treatment of catatonia. This Cochrane review was conducted with the aim of summarising higher-quality evidence from clinical trials to help guide clinical decision making in treating catatonia. However, the findings also raise the question of what constitutes feasible high level evidence for the treatment of acute emergency presentations such as catatonia.

**Methods**

This Cochrane review (Zaman 2019) aimed to assess the efficacy of benzodiazepine treatment compared with other drugs, placebo or ECT for catatonia in people with schizophrenia or severe mental illness (SMI), specified in the Cochrane review as bipolar affective disorder or depression. Inclusion criteria were double-blind randomised controlled trials (RCT) with participants diagnosed with catatonia alongside schizophrenia or other SMI. Quasi-randomised studies were excluded. Interventions included benzodiazepines of any type, compared with any other pharmacological agent, placebo or ECT. This was not limited by dose, frequency or route of administration.

The first of the primary outcome measures was a 50% improvement in symptoms as measured using a Visual Analogue Scale (VAS; Box 2). Additional primary outcome measures included the duration of hospital admission, change in satisfaction and the incidence of clinically important adverse effects.

Electronic searches were performed using Cochrane Schizophrenia’s study-based register of trials using the terms “Catatonia” (under Health Care Condition) AND “Benzodiazepine” (under Intervention) (Box 3). The references of the included studies were inspected for further relevant studies. Citations were independently inspected by three review authors to identify relevant abstracts. The search results were appropriately displayed as a flow diagram. The risk of bias was independently assessed by two study authors using standardised criteria from the Cochrane Handbook for Systematic Reviews of Interventions. Overall, this review used an appropriate search method and included discussions of how they intended to further analyse their data for heterogeneity if multiple studies were included. The consistency of the methodology used compared to the previous search in 2007 allows for direct comparison.

**Results**

There were no new records identified compared to the previous empty-review. However, data was analysed from one of the studies that was previously awaiting assessment to resolve disagreements between investigators (Schmider 1999). This was a direct comparison between two benzodiazepines, lorazepam and oxazepam - two short-acting agents with similar pharmacokinetics but differing pharmacodynamics. Twenty-one participants were originally recruited for the study, of which 17 were included in the final analysis. The mean age of participants was 50.8 years (range 21-77 years) with a range of mental illness diagnoses. There was no difference in catatonia symptoms between treatment groups as defined by at least a 50% improvement on VAS (RR 0.95, 95% CI 0.42-2.16; n=17) or average total score on VAS (MD 1.18, 95% CI -1.99-4.35; n=17).

The quality of evidence was very low due to the small number of participants and risk of bias. It was of short duration (three days) whereby baseline observations were undertaken on day 1, the intervention received on day 2, and participants crossed over on day 3. Participants received lorazepam 2mg sublingually (n=7) or oxazepam 60mg sublingually (n=10) before being crossed over to the alternative treatment on day 3. Intramuscular and sublingual routes of benzodiazepine administration may be preferred to oral in catatonia due to concerns over oral intake and the safety of swallowing, the latter being a less restrictive intervention. Of note, sublingual benzodiazepines are not licensed for use in the UK. The included study used 2mg lorazepam, the equivalent of 20-40mg oxazepam and a dose much lower than is used in clinical practice in the treatment of catatonia. However, the other group were administered 60mg of oxazepam – approximately twice the equivalent dose of benzodiazepine compared to the lorazepam group. The choice of oxazepam dose was documented as being as per the manufacturer’s advice. The degree of catatonic symptoms was the only outcome measure that was reported in this study.

There was no discussion on if and how participants were randomised. However, it did state that the study was of a “double-blind” design. The method by which allocation was concealed was not discussed. The study was therefore rated high for selection bias. It was also rated as having an unclear risk of attrition bias, with four participants (19%) not included in the final analysis. Adverse reactions were not reported and the study was therefore deemed to have an unclear risk of reporting bias.

The cross-over interval was short. This was explained by the author(s) as being due to ethical reasons to prevent a prolonged unmedicated period between interventions. However, even with short acting benzodiazepines such as lorazepam and oxazepam, the pharmacokinetics of these drugs means a carry-over effect cannot be excluded. This review accounted for this by only using data from the first arm of the trial. Moreover, the cited ethical reasons also bring the appropriateness of the cross-over design into question. Such a design may have the advantage of reducing the sample size needed to adequately power the study, but would be more suited to a disease that is both chronic and stable, unlike catatonia which can change rapidly (Box 4).

**Discussion**

This review included a single study that compared two benzodiazepines in the treatment of catatonia. This was very low-quality evidence due to having a small sample size, short duration and numerous sources of bias. The reasons for the limited findings may be from a genuine lack of randomised trials, but one cannot exclude bias within the search methodology that fails to identify relevant studies. The authors, quite rightfully, recognise that some randomised trials may not have been included based on the lack of clarity about the study design or inappropriate use of statistics and outcome measures. This outcome most likely reflects the scarcity of research into catatonia, either due to difficulties in study design and/or interest into the field. One could suppose that with improvements in early intervention services and a wide array of choice in psychotropic agents for affective and psychotic disorders, that catatonia may be less common (though without reliable epidemiological data this is conjecture). In psychiatric settings, catatonia is only seen in extremis; a life-threatening presentation that requires immediate treatment, often in patients that are not capacitous to consent. It may also be that catatonia continues to be under-recognised and under-diagnosed. This is further compounded by the differing diagnostic criteria within the most commonly used classifications of the Diagnostic and Statistical Manual for Mental Disorder (DSM-V) and the International Classification of Diseases (ICD-10) (Box 5).

While this review highlights the paucity of RCT’s on the use of benzodiazepines in catatonia, this does not necessarily equate to a lack of an evidence-base (box 6). With case series’ (Mekala 2020, Neerukonda 2020, Petrides 1997) and observational studies (Raveendranathan 2012) demonstrating their efficacy, the use of placebo controlled trials for an acute, life-threatening state could arguably be both dangerous and unethical. While RCT’s are held high quality evidence (Figure 1), this raises the question about whether RCT’s are either necessary or appropriate to understand the role of benzodiazepines in treating catatonia. It is important that epidemiological studies are undertaken to establish the burden of catatonia in psychiatric settings. Also, an improved understanding of the pathophysiology and neural circuitry may elucidate new targets for treatment.

The sublingual route of administration as well as low dose of lorazepam and non-equivalence of the dose of oxazepam used means that applicability of this study was also poor. Oxazepam is an agent that is rarely used in clinical practice. There were no studies that used benzodiazepines with differing pharmacokinetics such as diazepam and clonazepam or trials that have compared this group of medications to alternative psychotropic agents, placebo or ECT.

The single study included in this Cochrane review used the outcome measure of a 50% improvement

in symptoms, according to the VAS. This is traditionally used in the assessment of pain and has not be

validated for use in catatonia. The sensitivity and specificity is therefore unclear. Alternative tools to

screen for and monitor the progression of catatonic signs and symptoms include the Bush-Francis

Catatonia Rating Scale and the Northoff Catatonia Scale, both of which have been shown to be reliable

and sensitive to change (Bush 1996a, Bush 1996b, Northoff 1999). These tools were available at the

time of study and it remains unclear why these rating scales were not used. This was not discussed by

the authors in the original article (Schmider 1999). A lack of recognition of these validated tools may

be another contributory factor to the under-diagnosis of catatonia.

Catatonia is a core presentation of NMDA receptor encephalitis, indicating that the immune system may be important in its pathophysiology and that immunomodulatory therapy may be an effective treatment (Rogers 2019). This includes the use of plasmapheresis, intravenous immunoglobulin, corticosteroids or rituximab (Rogers 2019). It remains to be seen whether novel interventional techniques may assist in more targeted treatments for catatonia such as repetitive Transcranial Magnetic Stimulation. This has already been published in several case reports (Kate 2011, Takamiya 2015, Shiozawa 2013) and represents an exciting prospect. The slow onset of its efficacy means that it’s clinical use will likely be limited to patients unresponsive to benzodiazepines, where ECT is either contraindication or not available or where long-term maintenance treatment is required (Hansbauer 2020). it may also enable a more in depth understanding of the cortical and subcortical motor circuits that are implicated in the pathophysiology of this complex and potentially life-threatening phenomenon. TMS has already shown promise in specifically targeting the dorsolateral prefrontal cortex to treat depression; one of the most common causes of catatonia. With enhanced understanding of the neural circuits of interest, rTMS could provide an adjunctive or alternative treatment for catatonia without the risk of dependency or the need for a general anaesthetic.

**Conclusions**

The findings of this review are not able to influence clinical practice. However, they do highlight the paucity of high-quality evidence for the management of this potentially life-threatening syndrome that can manifest as a feature of numerous mental disorders. It raises an interesting discussion about why this may be the case including difficulties with recognition and diagnosis and about study design. Specifically, one is left wondering what constitutes high level evidence for the acute treatment of catatonia and whether RCT’s are both feasible or appropriate. Improved awareness about validated diagnostic tools and better concordance between classification systems may improve rates of diagnosis and subsequent epidemiological data about the prevalence of catatonia. Future randomised or observational studies ought to ensure that any pharmacotherapy used is clinically relevant (including formulation, dose, frequency and route of administration) to improve generalizability. It remains unclear whether benzodiazepines are superior to alternative agents, placebo or ECT and if so, which formulation, dose and regimen is optimal.

**Boxes**

Box 1: Organic causes of catatonia

Like most neuropsychiatric symptoms, catatonia can occur secondary to organic pathology including infectious (e.g. meningitis and encephalitis), autoimmune encephalitis, metabolic (e.g. homocystinuria and hepatic encephalopathy), benzodiazepine withdrawal and structural disorders (e.g. stroke). It is therefore crucial that clinicians consider a wide differential diagnosis as to the aetiology of acute onset catatonia.

Box 2: Visual Analogue Scales

A Visual Analogue Scale (VAS) is an external and objective assessment of variables that cannot be otherwise directly measured. This predominantly measures the intensity of symptoms that lie on a continuum as opposed to being categorical. It is widely used in the assessment of pain but can also be applied to the symptoms of catatonia that are described in Table 1.

Box 3: Cochrane Schizophrenia’s study-based register of trials

This register was developed in 1994 and is regularly updated through systematic searches of online databased, hand-searching of literature, searching grey literature, email alerts, checking references of relevant papers and their citations and by contacting relevant researchers and organisations. This database is compiled using multiple electronic databases without limitations on language, date, document type or publication status. As of May 2018, it contains 25,328 reports for 18,079 coded studies. It includes studies where randomization is either described or implied and includes quasi-randomised and non-clinical studies. The register can only be accessed by the Information Specialist on behalf of Cochrane Schizophrenia Group authors.

Box 4: Cross-over trials

Cross-over studies are longitudinal studies that can be observational or interventional in nature. They have a repeated measures design where each participant receives a sequence of two interventions (which may include a placebo). All participants therefore receive the same number of treatments for the same duration. The advantage is that fewer participants may be needed to adequately power the study. However, this design may not be feasible for acute and rapidly changing clinical conditions such as catatonia. It is more suitable for chronic and stable conditions, the aim of which is improved quality of life as opposed to cure. After all, if the first treatment cures the patient then the second will not have a chance to demonstrate its efficacy. It is also a commonly used trial design for bioequivalence studies.

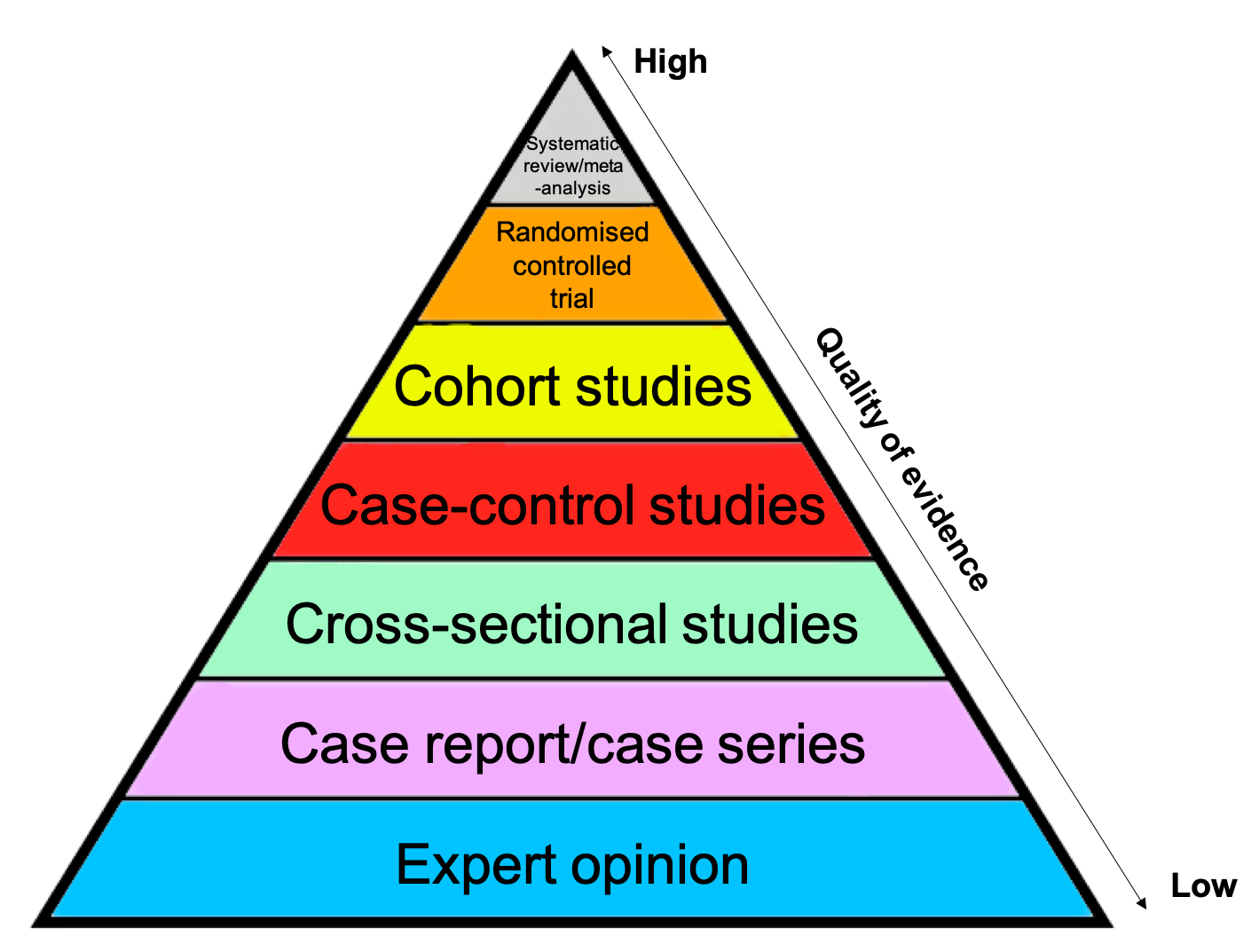
**Box 5: Classification of catatonia**

Catatonia is classified differently within the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and the International Classification of Diseases (ICD-10). Within the DSM-V, catatonia is coded under 293.89 as a specifier as being associated with another mental disorder (119), catatonic disorder due to another medical condition (120) or unspecified catatonia (121). Within the ICD-10, catatonia is coded as either an organic catatonic disorder (F06.1) or catatonic schizophrenia (F20.2). Catatonia is therefore a recognised specifier across a wider spectrum of primary psychiatric disorders in the DSM-V than the ICD-10.

Box 6: Evidence Based Medicine (EBM)

Evidence based medicine describes the use of clinical research in solving clinical issues, including diagnosis, treatment, risk of adverse effects, prognosis and causation. As well as incorporating the hierarchy of evidence described in figure 1, it also stresses the importance of using this in the context of the individual patient, their wishes and values, as well as the risks and benefits of each intervention for that person. This review highlights a clinical scenario where study design is difficult, and therefore the objective evidence base is scant. Clinical practice then becomes informed more by experience than by evidence. Nonetheless, it is very important not to misinterpret the absence of evidence as evidence of null effect and for clinicians to be supported not only in the use of EBM in forming clinical guidelines, but also in their implementation, and how to approach situations of uncertainty.

**Figures**



**Figure 1:** hierarchy of evidence. This describes the study designs with the highest quality evidence to the lowest quality that may then be used to inform clinical decisions and guideline formation.

**Tables**

**Table 1:** four categories of signs and symptoms of catatonia (Walther 2016)

|  |  |
| --- | --- |
| Symptom category | Examples |
| Motor signs | Posturing Rigor Immobility |
| Disturbance of volition | Ambitendency Negativism Automatic obedience Mutism Withdrawal Stupor |
| Disinhibition | Stereotypies Mannerisms Rituals Echolalia Echopraxia Verbigeration Perseveration |
| Autonomic instability | Tachycardia Hyperthermia |

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