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Lorazepam in catatonia – Past, present and future of a clinical success story

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ABSTRACT

The effect of lorazepam in the treatment of catatonia is outstanding and almost immediate. Clinicians are familiar with its effects: mute patients can speak again, akinetic patients can move again and patients with negativism can eat and drink again within usually a short duration of about 10 min to 1–2 h. Fear is often gone after lorazepam administration. While not always effective, the introduction of lorazepam into clinical practice represented a breakthrough and was often life-saving for many patients suffering from catatonia. It is rare to observe such rapid therapeutic effects in other domains of psychiatry. In this narrative review we will briefly look at the past, present and future of lorazepam in the treatment of catatonia. It is gratifying to reflect on the fact that clinicians using the age-old medical practice of observation and empirical treatment succeeded in advancing the management of catatonia 40 years ago. The present evidence shows that the clinical effect of lorazepam in catatonia treatment is excellent and more or less immediate although it remains to be explicitly tested against other substances such as diazepam, zolpidem, clozapine, quetiapine, amantadine, memantine, valproate and dantrolene in randomized clinical trials. In addition, future studies need to answer the question how long lorazepam should be given to patients with catatonia, months or even years? This narrative review promotes the rapid use of lorazepam in the treatment of acute catatonic patients and stipulates further scientific examination of its often impressive clinical effects.

1. Past: brief history of lorazepam in catatonia and how it all began

The history of lorazepam and its use in the treatment of catatonia is instructive and exciting, but this successful development was by no means foreseeable in the 1970s. The road to such an effective drug was initially rather rocky (Mendelson, 2020) and to better understand the development of this clinical success story, it is important to look at the origins of this catatonia treatment. Before the introduction of lorazepam (or other benzodiazepines) into clinical practice, psychiatrists used amobarbital sodium (amytal) (Garry, 1932) often with dramatic results not necessarily at high doses, setting the precedent - presumably by the same GABA mechanisms - for lorazepam (Bleckwenn, 1931; Thorner, 1935). Catatonia patients not responding to amytal were treated with high doses of camphor or pentylenetetrazol (Metrazol) inducing seizures (Fink and Taylor, 2009; Gazdag et al., 2009; Meduna, 1935).

From a historical perspective, barbituric acid (malonyl urea) was first synthetized in 1864 by J.F.W. Adolph von Baeyer (1835-1917) (Cozanitis, 2004). The first synthesis of a new hypnotic called barbital was by German chemists Emil Fischer (1852-1919) and Josef von Mering (1849-1908) (Fischer and v Mering, 1903). In 1923, Horace Abbott Shonle (1892-1947), who was director of organic chemical research for Eli Lilly & Co., synthesized amylobarbitone (Amytal) (Shonle and Moment, 1923) (for historical overview see (Cozanitis, 2004). Amytal was widely used as a sedative and hypnotic to treat anxiety, insomnia, chronic pain, epilepsy and alcohol withdrawal in the 1930s. The history of catatonia treatment with amytal dates back to the early 1930s as well, when an American neurologist and psychiatrist William Jefferson Bleckwenn (1895-1965) first introduced the use of sodium amytal for treating catatonia (Gershon and Shorter, 2019; Bleckwenn, 1931). Bleckwenn showed that by injecting sodium amytal into the bloodstream, the catatonic state could be lysed resulting in resolution of mutism and motor signs (Bleckwenn, 1931). Since then, several other physicians explored the use of amytal for diagnosis and treatment of catatonia (Broder, 1937; Thorner, 1935). For instance, in 1950s, Elkes (Elkes, 1957) as well as Stevens and Debyshire (Stevens and Derbyshire,

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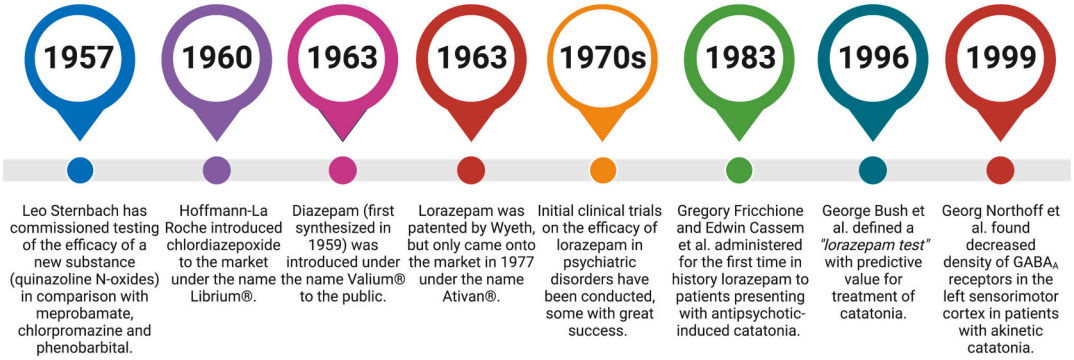

Fig. 1. Important milestones in the history of lorazepam and catatonia treatment.

1958) investigated the use of amytal in the diagnostic assessment of catatonic patients (see also articles on amobarbital interview in different psychiatric disorders (Ilechukwu and Henry, 2006; Kavirajan, 1999; Naples and Hackett, 1978; Ruedrich et al., 1985; Stiebel and Kirby, 1994; Wettstein and Fauman, 1979)). In particular, the amytal interview was a diagnostic assessment that was done by administering a sedative drug, such as sodium amytal, to the patients to assess their unconscious conflicts and thoughts. During the amytal interview, the psychiatrist asked the patient questions about their thoughts and feelings related to the presenting problem. The patient's responses were then used to gain insight into their psychological state, as well as to identify any underlying psychological issues which might have contributed to the problem. However, amytal fell out of favor in the 1950s due to its addictive potential and narrow therapeutic window (Dunlop, 1970; Goldstein, 1947).

In 1950s, Leo Sternbach (1908–2005), who was initially trained in organic chemistry at Krakow University and worked as a Hoffmann-La Roche chemist, was commissioned to develop new drugs as competitors to a tranquillizer called meprobamate (Mendelson, 2020). Meprobamate was discovered by Frank Milan Berger (1913–2008) in 1954 and launched on the US market under the name *Miltown* in 1955. Although Sternbach was initially unable to deliver promising results and had to switch to the development of antibiotics, he did achieve a breakthrough in 1957 (Mendelson, 2020). He developed an active compound that could reduce aggression, relieve anxiety and relax muscles. Furthermore, Sternbach re-analyzed its chemical structure and found that it belonged to the family of benzodiazepines (=benzene ring and diazepine nucleus) (Sternbach et al., 1963). He called this compound chlordiazepoxide. In 1960, Hoffmann-La Roche introduced chlordiazepoxide to the market as *Librium*® (Wick, 2013; Sternbach, 1972). Three years later, in 1963, diazepam (first synthesized in 1959) was introduced under the name *Valium*® (Sternbach, 1978). In the same year, lorazepam was patented by Wyeth (formerly American Home Products), but only came onto the market in 1977 under the name *Ativan*® (Gluckman, 1971). Nevertheless, in the early 1970s, scientists began to investigate effects of lorazepam that differ from diazepam in human studies (Haider, 1971; Schrappe, 1971). According to PubMed, one of the first double-blind study on the efficacy of lorazepam in comparison to 100 mg sodium pentobarbital in humans was published in 1971 by Elliott et al. (Elliott et al., 1971): Elliott et al. examined the sedative-hypnotic activity of single oral doses (2.5 mg–7.5 mg) of lorazepam in a group of 15 healthy adult men. Shortly after, psychiatrists began using lorazepam (*Ativan*® or *Tavor*®) in the treatment of patients with mental illness, especially sleep disorders, anxiety neurosis and psychosis (Coates, 1972; Haider, 1972; Kaemmerer, 1972). For instance, Guz et al. (Guz et al., 1972) administered haloperidol (3 mg/day) and lorazepam (6 mg/day) or placebo to 60 patients with acute psychosis in a double-blind clinical trial. The authors showed a trend in favor of the lorazepam-treated group (non-significant results, $p > 0.05$) and concluded that lorazepam might have some benefit on individual clinical symptoms (Guz et al., 1972).

Then in 1983, lorazepam was used for the first time in the treatment of patients with antipsychotic-induced catatonic syndrome. In the case study of Fricchione and Cassem et al. (Fricchione et al., 1983), four patients seen on the Massachusetts General Hospital Psychiatry Consultation Service suffering from catatonic reactions (e.g. catalepsy, muscular rigidity, waxy flexibility, mutism, negativism, staring and bizarre behavior) to antipsychotics were described. The first patient treated had been given haloperidol by one of our authors (GF) for post-operative agitation. The patient subsequently became catatonic. It was GF's mentor, the late Dr. Edwin Cassem, summoned in the evening by GF after anti-cholinergic medication failed to provide relief, who decided to give intravenous (IV) lorazepam a try leading to a rapid and dramatic lysis of all catatonic symptoms. All four patients reported were treated with 2 mg of IV lorazepam. Within few minutes, all patients experienced a significant improvement in their catatonic symptoms, they were able to speak, eat, drink and move again. The authors concluded that whenever a patient develops a catatonic-parkinsonian response to antipsychotics, a trial of lorazepam given IV, may be warranted because of its rapid onset, duration of action and relative safety (Fricchione et al., 1983). Furthermore, Fricchione et al. (Fricchione et al., 1983) recommended lorazepam as a treatment for other forms of catatonia as well: *"It might also be worthwhile to study its effectiveness in other selected subtypes of catatonia, including those secondary to affective disorders and schizophrenia."* This early work led to increased interest in research of lorazepam as a treatment option for psychogenic catatonia (Ripley and Millson, 1988; Salam and Kilzieh, 1988), catatonia associated with affective psychosis (Greenfeld et al., 1987) and catatonic schizophrenia (Ahuja, 1988; Wetzel and Benkert, 1988), respectively. Finally, the rapid acute response to low dose lorazepam (1-2 mg) has since been observed in various clinical studies on catatonia (see (Northoff et al., 1995; Pelzer et al., 2018), (Edinoff et al., 2021), and (Rasmussen et al., 2016) for details)). Taken together, the pharmacological and clinical history of lorazepam is not only interesting, but also represents the continued utility of empiric therapeutic trials (see Fig. 1 for historical overview).

2. Present: clinical use and GABAergic mechanism of action

Lorazepam is a drug from the group of benzodiazepines and has anxiolytic, sedative (calming), muscle-relaxing and anticonvulsant effects. Lorazepam has an FDA-approved indications for short-term (4 months) relief of anxiety symptoms, anxiety-associated insomnia, anesthesia premedication in adults and Treatment of status epilepticus (Ghiasi et al., 2022). Non-FDA-approved indications include agitation, alcohol withdrawal delirium, alcohol withdrawal syndrome, insomnia, panic disorder, delirium, chemotherapy-associated anticipatory nausea, and vomiting (adjunct or breakthrough), as well as psychogenic catatonia (Ghiasi et al., 2022). Lorazepam can be administered as an oral (OS), IV or intramuscular (IM) preparation. After OS sublingual administration time of peak concentration is approximately 2 h

(Greenblatt et al., 1982). Lorazepam IV administration takes effect after 1–3 min, lorazepam IM administration takes effect after 15–30 min (Ghiasi et al., 2022; Greenblatt et al., 1982; Greenblatt et al., 2000). Although the majority of case reports and clinical studies reported the daily dosage of lorazepam in catatonia treatment, we lack randomized controlled trials examining frequency of lorazepam administration and outcomes. Due to its elimination half-life of 14 ± 5 h, 2–3 dosages per day (every 4–12 h) are recommended to achieve a therapeutic effect (Daniels, 2009; Ghiasi et al., 2022).

From a pathophysiological point of view, lorazepam's target structures, as is the case with most benzodiazepines, are GABA (gamma-amino-butyric acid) receptors in the central nervous system. In particular, lorazepam binds to a specific modulatory site of the $GABA_A$ receptor, the benzodiazepine binding site which enhances the inhibitory effect of GABA. Technically, benzodiazepines are positive allosteric modulators of the $GABA_A$ receptor, rather than its agonists. As a result, the inhibitory effect of the neurotransmitter GABA is enhanced. Interestingly, positive allosteric modulation at the $GABA_A$ receptor with lorazepam induced higher signal decreases in OFC (Richter et al., 2010). This means that the application of lorazepam can compensate for the OFC dysfunction and lead to improved emotional regulation in patients with catatonia. Further, administration of the $GABA_A$ receptor agonist lorazepam might directly ameliorate GABAergic deficits in premotor and primary motor cortices (M1) (Di Lazzaro et al., 2000; Northoff, 2000; Northoff et al., 1995). Since GABA is one of the main inhibitory neurotransmitters within the M1, the application of lorazepam or electroconvulsive therapy (ECT) may lead to an increased activation of GABA-related inhibitory circuits in M1 (Bello et al., 2017; Di Lazzaro et al., 2000; Moskowitz, 2004). This assumption is also supported by a case report that showed a successful amelioration of catatonic symptoms following ECT and at the same time an increase of intracortical inhibition (ICI) (possibly due to an increases in GABAergic transmission) as determined by double-pulse transcranial magnetic stimulation (Dresler et al., 2010). This said, lorazepam has a similar effect as ECT and both can balance the ICI of the partially overactivated motor regions - as we can observe in patients suffering from catatonic symptoms (Walther et al., 2017a; Walther et al., 2017b) or dystonia (Lizarraga et al., 2016). The ventromedial prefrontal cortex (vmPFC), encompassing the orbitofrontal cortex (OFC; BA11,12), and rostral and subgenual anterior cingulate cortex (BA 25, 24, 32), is known to play a key role in the fear conditioned response that is the hallmark of the catatonic syndrome (Fricchione and Beach, 2019; Milad and Quirk, 2002; Stevens et al., 2011). Given that the OFC and other areas of vmPFC are strongly involved in emotion processing, which is GABAergic mediated (Taylor et al., 2019), these findings provide further evidence for GABAergic mechanisms in catatonia including both $GABA_A$ (decrease) and $GABA_B$ (increase) receptors (Hirjak et al., 2021; Northoff, 2002a, 2002b; Plevin et al., 2018). In line with this, Kline et al. (Kline et al., 2022) showed that patients diagnosed with schizophrenia related catatonia experienced significant anxiety and depression co-morbidities. The authors concluded that a significant relationship between GABAergic dysfunction and schizophrenia, catatonia, and affective dysregulation exists (Kline et al., 2022). Taken together, empirical evidence suggests the following: (i) alterations in $GABA_A$ and possibly $GABA_B$ receptors in catatonia; (ii) changes in emotion-related activity in limbic-cortical regions like the OFC and vmPFC as well as in sensorimotor cortex as parts of the catatonia-related cortico-striato-thalamo-cortical circuits; and (iii) emotion-motor interaction is GABAergic mediated. Together, these findings speak for primarily psychomotor (GABAergic, glutamatergic and serotonergic) mechanisms of catatonia as distinguished from purely motor and more exclusively dopaminergic mechanisms (Hirjak et al., 2022; Northoff et al., 2021; Northoff et al., 1999a; Northoff et al., 1999b).

In a clinical routine, lorazepam can also be administered for diagnostic purposes. One can use a 2 mg dosage once or twice for what recently has been operationalized as a “Lorazepam challenge test” (LCT) (Suchandra et al., 2021). More precisely, LCT is a simple and cost-effective method of accurately diagnosing catatonia. To perform a LCT, one (or two) doses of 1–2 mg IV lorazepam is usually administered and the patient is then assessed for response after 5 min using a clinical catatonia rating scale. A significant reduction (e.g. at least 50 %) in catatonic signs and symptoms on a clinical rating scale is considered a positive LCT (Sienaert et al., 2014). Therapeutic effects are quite high and response percentages from 66 % up to 100 % have been reported (Edinoff et al., 2021; Northoff et al., 1995; Rasmussen et al., 2016; Rosebush et al., 1990). The majority of these studies has mainly been conducted in the western world. Studies conducted in India and Asia show a larger response-non-response range from 0 % to 100 % (Pelzer et al., 2018; Seetharaman et al., 2021; Tibrewal et al., 2010), but the exact reason for these differences remains unclear. Usually, administration of lorazepam is well tolerated. For adolescent and adult patients with severe catatonia, higher doses of 16 to 30 mg/d for 3–5 days have occasionally been necessary and well tolerated without showing any sedation or major side effects (Bush et al., 1996a; Fink, 2001; Pelzer et al., 2018). However, in elderly catatonia patients, very high doses of lorazepam may not be tolerated because of sedation. A PubMed search with the terms "catatonia" AND "lorazepam" AND "elderly" in the title or abstract on January 29th 2023 yielded five references (e.g. (Takata et al., 2005). It is noteworthy that these articles did not report on the effects of very high doses of lorazepam and their side effects in elderly patients. The vast majority of elderly patients mentioned were treated with standard dose lorazepam. Overall, the evidence on catatonia and its treatment in elderly is very limited (for review see (Kaelle et al., 2016; Serra-Mestres and Jaimes-Albornoz, 2018; Swartz and Galang, 2001; Takata et al., 2005). Therefore, in elderly catatonia patients, clinicians should also be aware of the interaction with other sedating, anticholinergic or antihypertensive drugs, because such polypharmacy can lead to sedation, delirium, worsening of cognitive functioning and possibly falls, respectively.

From a psychopathological point of view, therapeutic response includes partial or often even complete remission of catatonic symptoms within 4–5 days if not within the first day (or two days) (Rasmussen et al., 2016). The therapeutic response seems to be strongest in acute catatonia where patient present with a rapid onset catatonic picture (Edinoff et al., 2021; Northoff et al., 1995; Rasmussen et al., 2016; Rosebush et al., 1990). This applies especially to patients with bipolar disorder and major depressive disorder (Rasmussen et al., 2016). In contrast, patients with more chronic catatonia especially in the context of chronic schizophrenia show a less effective response to lorazepam and are more likely to receive ECT (Pelzer et al., 2018; Rasmussen et al., 2016; Ungvari et al., 1999). Interestingly, according to scientific evidence, lorazepam has been found to be effective in improving a variety of catatonic symptoms including agitation, akinesia, mutism, stupor, rigidity, echolalia and flat affect. However, to the best of our knowledge, only one study has examined the level of reduction in individual catatonic sign severity associated with variable doses of IV lorazepam. Suchandra et al. (Suchandra et al., 2021) showed that stupor, mutism, staring, posturing, withdrawal, ambitendency and automatic obedience responded equally well to the first-dose 2 mg and 4 mg IV lorazepam.

However, according to the same study, echolalia, rigidity, negativism and Mitgehen responded significantly only to 2 mg of IV lorazepam, while Gegenhalten showed a selective response to 4 mg of IV lorazepam. Despite methodological limitations, this study provides preliminary evidence that lorazepam may have differential effects on catatonic symptoms. A PubMED search with the terms “mutism”, “akinesia”, “stupor” or “rigidity” AND “lorazepam” AND “response” in the title or abstract on January 29th 2023 yielded 14, 2, 9 and 12 hits respectively with partially overlapping studies/case reports. Another PubMED search with the terms “mannerism”, “aggression”, “flat affect”, “agitation” or “echolalia” AND “lorazepam” AND “response” in the title or abstract on January 29th 2023 yielded 0, 7, 1, 31 and 3 hits respectively with some overlapping studies/case reports as well. Taken

together, this suggests that few studies have examined the differential therapeutic effects of lorazepam (at different doses) on specific catatonic symptoms. What weakens the conclusion of these studies is that they had other primary endpoints aside from improvement of specific catatonic symptoms and did not focus mainly on the above-mentioned clinical question.

Still, it is evident that lorazepam helps in both retarded/stuporous/akinetic (Gaind et al., 1994; Northoff et al., 1999b; Parekh et al., 2022; Wahidi and de Leon, 2018) and excited catatonia (Burns et al., 2021; Neerukonda et al., 2020; Pruett and Rizvi, 2005; Tseng and Huang, 2018; Zain et al., 2021). Furthermore, based on recent studies, it is also evident that lorazepam is effective in catatonia associated with different psychiatric and neurological disorders such as autism, intellectual disability, schizoaffective disorder, COVID-19 infection and Anti-N-Methyl-D-Aspartate Receptor Encephalitis, respectively. But, we are still missing a randomized, double-blind clinical trial investigating the effects of different doses of lorazepam in patients with akinetic or hyperkinetic/excited catatonia. Therefore, a clinical trial to systematically examine catatonia symptoms before and after therapy with lorazepam using the Northoff Catatonia Rating Scale (NCRS) (Northoff et al., 1999a), with its extensive array of both psychological and motoric signs, or the Bush-Francis Catatonia Rating Scale (BFCRS) (Bush et al., 1996b), is warranted to see exactly which domains/symptoms have improved or worsened. We also strongly acknowledge that the same should be done with other medications used for catatonia to be able to see differential effects of different substance classes.

Overall, it is not entirely clear from the evidence why the majority of studies on catatonia patients have used lorazepam. Possible reasons include the peak plasma concentration after 3 h, high availability in the circulation after oral administration (80–100 %), the half-life of 10–20 h, reaching steady-state already after 3 days, and prolonged clinical effects after IV administration because of less rapid and extensive drug distribution compared to diazepam (see Greenblatt and Shader for more details (Greenblatt and Shader, 1978; Greenblatt et al., 2000)). Although other benzodiazepines such as diazepam (Huang, 2005; Huang et al., 2013), oxazepam (Schmider et al., 1999) and clonazepam (Kumar, 2001; Rice et al., 2021) have been used successfully in the treatment of catatonia, there is a lack of randomized, double-blind clinical trials comparing the efficacy of lorazepam with other benzodiazepines. According to the last Cochrane Database Systematic Review on benzodiazepines for catatonia (Zaman et al., 2019), to date, only one study has directly compared lorazepam and oxazepam in psychogenic catatonia with psychomotor slowing and mutism (Schmider et al., 1999). Schmider et al. (Schmider et al., 1999) treated 21 patients, with conditions characterized by severe psychomotor retardation and mutism, with 2 mg lorazepam and 60 mg oxazepam in a double-blind crossover study design lasting three days. Seven patients received lorazepam on day 2 and oxazepam on day 3 (LO-OX group), and 10 patients received oxazepam on day 2 and lorazepam on day 3 (OX-LO group). Both benzodiazepines significantly improved psychomotor retardation on day 2, but on day 3 none of the seven patients receiving oxazepam improved >50 % in psychomotor symptoms. This said, there was a significant difference between the treatment groups on day 3. The authors assumed that there might be an antagonizing lorazepam effect leading to a reduced response to other benzodiazepines (for details on this hypothesis see also (Curran et al., 1987)). Finally, the authors concluded that lorazepam and oxazepam are both effective in the treatment of psychomotor retardation and mutism. Furthermore, earlier studies by Ungvari et al. (Ungvari et al., 1994) and Bush et al. (Bush et al., 1996a) reported ECT to be superior to benzodiazepines in patients who failed to respond to lorazepam. Another study by Girish and Gill (Girish and Gill, 2003) compared ECT with risperidone in lorazepam non-responsive catatonia patients. This study examined 18 patients with non-affective catatonia, which did not respond to at least five-day trial of lorazepam (6–8 mg/day). The patients were than randomized into either ECT plus placebo (ECT group; $n = 8$) or sham ECT plus risperidone (risperidone group; $n = 6$) group. After three weeks, both groups showed improvement in catatonia symptoms according to BFCRS. The symptom improvement was greater in ECT group compared to risperidone group at any treatment week ($p = 0.035$). Furthermore, Unal et al. (Unal et al., 2017) examined 60 catatonia patients who received lorazepam and/or ECT. 55 patients (91.7 %) were initially treated with lorazepam and 5 patients (8.3 %) received ECT as the first-line treatment of catatonia. Thirteen (23.7 %) catatonia patients, which were initially treated with lorazepam improved, whereas 42 patients (70 %) showed no or only partial remission of their catatonic symptoms. These patients were consequently treated with both lorazepam and ECT (Unal et al., 2017). With the combination therapy of lorazepam and ECT, 39 patients (92.9 %) improved, but 3 patients (7.1 %) showed no or only little improvement of catatonic symptoms. In a more recent retrospective study, Wachtel (Wachtel, 2019) treated autism patients with catatonia who did not respond to lorazepam (1-27 mg/day) with ECT (16–688 sessions). ECT led to significant improvement in catatonic symptoms including treatment-resistant self-injury. Both studies demonstrated that ECT is a safe and effective treatment for lorazepam-resistant catatonia in different psychiatric disorders, with a high rate of response and few adverse effects. ECT should be considered when a 48-72 h lorazepam trial is unsuccessful (Fricchione, 1989). Still, studies examining the percentage of patients who failed lorazepam treatment and then go on to respond to ECT or antipsychotics are rare, because the majority of the clinical studies on catatonia continue a combination therapy of benzodiazepines and ECT (assuming synergistic therapeutic effects; for details see (Petrides et al., 1997)) after unsuccessful monotherapy with benzodiazepines. In particular, assuming that catatonia is a hypodopaminergic condition, then, lorazepam could ameliorate a hypodopaminergic state and ECT may increase the dopamine receptor sensitivity in the basal ganglia leading to improvement of akinesia (Balldin et al., 1982; Petrides et al., 1997). Overall, further research is needed to evaluate the safety and efficacy of ECT in benzodiazepine-nonresponsive catatonia, as well as its synergistic and long-term effects.

Besides benzodiazepines and ECT, zolpidem can also be used to treat catatonia. In 1995, Mastain et al. (Mastain et al., 1995) were the first to successfully use zolpidem to treat catatonia. However, only a few case reports (Bastiampillai et al., 2016; Kumar and Kumar, 2020; Peglow et al., 2013) have been published since then. There are no randomized controlled trials comparing zolpidem and benzodiazepines. Still, zolpidem in doses from 7.5 to 40 mg/d may be an option for patients who do not respond to benzodiazepines or ECT (Thomas et al., 1997).

Finally, a common clinical complication after the reduction or discontinuation of benzodiazepines is the so-called “benzodiazepine withdrawal catatonia”, which was first described in 1989 by Hauser et al. (Hauser et al., 1989). The case reports published afterwards described benzodiazepine (e.g. lorazepam, alprazolam, clonazepam, etc.) withdrawal catatonia in both psychiatric patients (Carroll, 1997; Deuschle and Lederbogen, 2001; Rosebush and Mazurek, 1996) and healthy elderly individuals (Kanemoto et al., 1999). These reports continue to stimulate the discussion about whether and when benzodiazepines should be discontinued after a full remission of catatonia. Several authors recommended lorazepam maintenance treatment for chronic or recurrent catatonia (Gaind et al., 1994; Manjunatha et al., 2007; Ripley and Millson, 1988; Thamizh et al., 2016). However, robust evidence on when benzodiazepines should be discontinued after full remission of acute catatonia is still lacking. This is another area of need for future studies. Such studies should first use retrospective data to examine the time from discontinuation of benzodiazepines to the appearance of the first catatonic symptoms (or admission to hospital). Further, patient-related outcomes including risks and benefits of discontinuation in terms of personalized medicine should also be recorded.

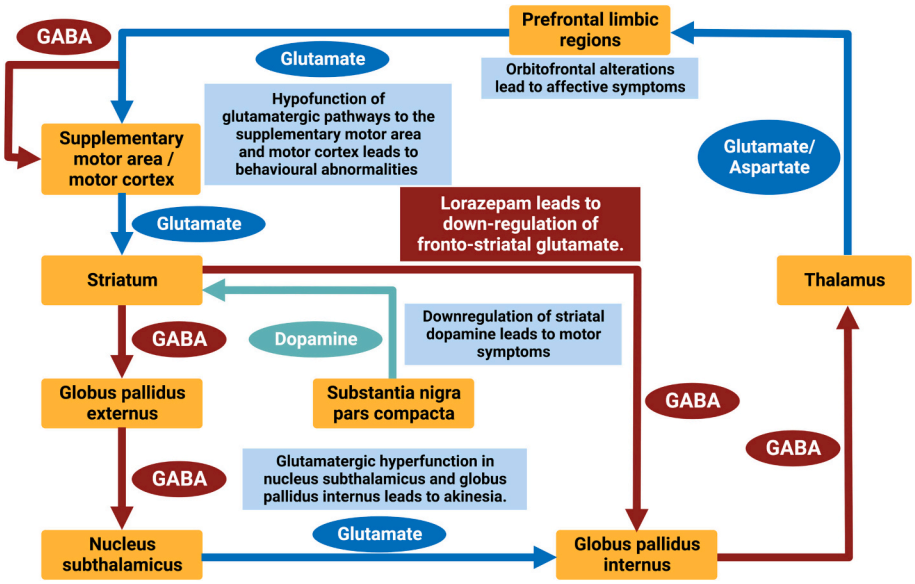

Fig. 2. GABAergic (inhibitory), glutamatergic (excitatory) and dopaminergic (inhibitory and excitatory) pathways underlying catatonia.

3. Future: urgent need of randomized-controlled clinical trials

Although lorazepam has an excellent effect on catatonic symptoms, some questions remain regarding its mechanism of action, efficacy and long-term use in routine clinical practice. First, it is still unclear which brain regions or networks are modulated by lorazepam (see also (Richter et al., 2010) for a first study). Another related question is what role do the $GABA_B$ receptors play in the pathophysiology of catatonia? Therefore, we strongly encourage future positron emission tomography studies on GABAergic system in catatonia. Second, the pathophysiological differentiation between genuine, substance- and withdrawal-induced catatonia is interesting and clinically highly relevant. Related is the question whether lorazepam can lead to additive effects in the long-term treatment of catatonia. Third, the question occasionally arises whether catatonia should be treated with benzodiazepines or other substances (e.g. haloperidol, risperidone, olanzapine and ziprasidone) especially in the context of co-morbid delirium. In managing chronic catatonic schizophrenia, a recent systematic review by Saini et al. (Saini et al., 2022) reported that over 80 % of reported catatonia patients (across both cohort studies and case reports) reached at least partial remission following treatment with clozapine. The therapeutic effect of clozapine and its primarily metabolite norclozapine in catatonia is probably due to low D_2 receptor affinity accompanied by relatively rapid D_2 receptor dissociation, inverse agonism to $5HT_{2A}$ receptors and modulation of glutamate/glycine and GABA transmission (Dursun et al., 2005; Ellul and Choucha, 2015; Melone et al., 2003; O'Connor and O'Shea, 2015; Seeman, 2014). In addition other psychotropic substances such as amantadine and memantine (*N*-methyl-D-aspartate antagonists) (Hervey et al., 2012)) or dantrolene (peripheral muscle relaxant not crossing blood-brain barrier) have also shown effectiveness in the treatment of malignant (febrile) catatonia, especially in patients that did not show a sufficient response to lorazepam (Fricchione, 1985; Northoff et al., 1997; Northoff et al., 1995; Schulte-Sasse et al., 1985; Stemp, 1993). Therefore, randomized-controlled clinical trials on the efficacy of lorazepam compared to other substances are desirable.

Generally speaking, several issues need to be considered when conducting large-scale double-blind randomized controlled clinical trials in catatonia patients. Patients with mild catatonic symptoms and the ability to consent are mainly treated at the psychiatric department and can be relatively easily included in a clinical or neuroimaging study. But, recruitment of patients with severe catatonic symptoms such as akinesia, mutism, anxiety and stupor or malignant catatonia might be very challenging. This group of patients needs to be treated in intensive care unit (ICU). Still, if one looks at the scientific evidence in patients with delirium in the ICU (Andersen-Ranberg et al., 2022), it should be feasible to conduct a well-powered and methodologically sophisticated clinical study with seriously ill catatonia patients, when considering their special circumstances. For instance, the enrollment and treatment of catatonia patients lacking the capacity to provide consent because of akinesia, mutism, anxiety or stupor might be allowed as an emergency procedure. Before enrollment of the patient, consent could be obtained from a surrogate decision-maker who represents the patient as a legal guardian in an institutional review board approved fashion. After enrollment oral and written informed consent can be obtained from this authorized patient representative to continue trial participation. Later on, when the capacity to provide informed consent has returned, the patient can be asked to give study consent (Andersen-Ranberg et al., 2022).

Finally, for clinicians, the question is how long patients with catatonia should take lorazepam. The potential of abuse and dependence and the cognitive dysfunction after long-term treatment with lorazepam play a major role in such considerations. However, the question of whether patients with catatonia can become dependent on lorazepam is controversial and has not yet been clarified. So far, no distinction has been made between physical and psychological dependence in catatonia cases. The question of whether lorazepam therapy can cause long-term cognitive impairment in patients with catatonia is far from clear, partially due to small and heterogeneous studies on this topic (Serrat et al., 2022; Stewart, 2005). It may also be that lorazepam rather improves cognition, in the sense of shortening the duration of untreated catatonia. This cognitive effect is thought to occur with the cognitive enhancer memantine, when used in the treatment in catatonia (Graziane et al., 2020).

Overall, many questions remain unanswered in the treatment of catatonia. At the moment given the present level of our knowledge, and given the effectiveness of lorazepam over the past 40 years in relieving the extraordinary suffering and the morbidity and mortality associated with the catatonic syndrome, benefits clearly outweigh the risks of its use. Nevertheless, we hope our narrative review will stimulate interest in many of our colleagues to conduct further studies on and for patients with catatonia.

Contributors

DH and GN: original idea and design of the commentary. DH: first draft of the manuscript. DH, GF, RCW and GN: discussion of the topic, writing and manuscript revision.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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