# Symptomatic treatment of children with anti-NMDAR encephalitis

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**ABBREVIATIONS**

| | |
|---|---|
| IVMP | Intravenous methylprednisolone |
| NMDAR | *N*-methyl-D-aspartate receptor |

**AIM** We performed the first study on the perceived benefit and adverse effects of symptomatic management in children with anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.

**METHOD** A retrospective chart review was undertaken at two tertiary paediatric hospitals in Australia and New Zealand. We included 27 children (12 males, 15 females; mean age at admission 7y 1mo) with anti-NMDAR antibodies in serum or cerebrospinal fluid with a typical clinical syndrome.

**RESULTS** Only two out of 27 patients were white, whereas 16 out of 27 patients were from the Pacific Islands/New Zealand Maori. The mean duration of admission was 69 days (10–224d) and 48% of patients (13/27) needed treatment in an intensive care setting. A mean of eight medications per patient was used for symptomatic management. Symptoms treated were agitation (*n*=25), seizures (*n*=24), movement disorders (*n*=23), sleep disruption (*n*=17), psychiatric symptoms (*n*=10), and dysautonomia (*n*=four). The medications used included five different benzodiazepines (*n*=25), seven anticonvulsants (*n*=25), eight sedatives and sleep medications (*n*=23), five antipsychotics (*n*=12), and five medications for movement disorders (*n*=10). Sedative and sleep medications other than benzodiazepines were the most effective, with a mean benefit of 67.4% per medication and a mean adverse effect-benefit ratio of 0.04 per medication. Antipsychotic drugs were used for a short duration (median 9d), and had the poorest mean benefit per medication of 35.4% and an adverse effect-benefit ratio of 2.0 per medication.

**INTERPRETATION** Long-acting benzodiazepines, anticonvulsants, and clonidine can treat multiple symptoms. Patients with anti-NMDAR encephalitis appear vulnerable to antipsychotic-related adverse effects. Pacific Islanders appear to have a vulnerability to anti-NMDAR encephalitis in our region.

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an antibody-mediated diffuse encephalitis that predominantly affects young adults and children. Children often present with behavioural symptoms and then develop distinctive movement disorders combined with seizures, encephalopathy, sleep disturbance, or dysautonomia.[1,2] The use of early immune therapy has improved the recovery rates in children and has been described in detail in the literature.[1] However, more than half of the patients require second-line immune therapy, endure prolonged hospital admissions, and require symptomatic management of this complex disorder. There is a small body of existing literature that discusses treatment of psychiatric symptoms[3–5] and intensive care management[6,7] in anti-NMDAR encephalitis. We undertook a retrospective study of symptomatic pharmacological management of all symptoms in children with this condition.

## METHOD

The use of medications for the symptomatic treatment of anti-NMDAR encephalitis was reviewed at two tertiary children's hospitals in Australia (Children's Hospital at Westmead, Sydney) and New Zealand (Starship Children's Hospital, Auckland). These two hospitals are the largest referral centres for children in New South Wales, Australia and New Zealand respectively.

Twenty-seven patients diagnosed prospectively (*n*=13) or retrospectively (*n*=14) with anti-NMDAR antibodies in either serum or cerebrospinal fluid with typical clinical syndromes were included in this study. All samples tested were from the acute phase of the illness. Cerebrospinal fluid antibodies were positive in all 21 patients tested. Cerebrospinal fluid was not available for six retrospectively diagnosed patients who were positive for antibodies in serum.

The patients had been treated by various paediatric neurologists in each department over a 15-year period. Ethics approval was obtained from the respective human research ethics committees. Some patients were identified and followed up as a part of a larger encephalitis study,[8] whereas follow-up information on other patients was obtained by correspondence, hospital records, and telephonic interview.

Maori patients from New Zealand were grouped with other patients from the Pacific Islands, including those from New Caledonia, as Pacific Islanders. A detailed chart review was done to identify demographic and medication details during the admissions and outpatient follow-up relating to the first episode of encephalitis only. We did not include subsequent admissions in three patients who had a relapse between 8 months to 2 years after the first episode. Each chart was reviewed by two reviewers at both sites, none of whom had been directly involved in the respective patient's clinical care. Where required, patient records were reassessed for consensus by two or more reviewers during final tabulation. Medications were grouped under major categories depending on their indication or mode of action (Table I and Table SI, online supporting information). We excluded medications used primarily for intensive care-related indications such as muscle relaxants and anaesthetizing agents such as propofol or thiopentone.

Perceived benefit from medications and adverse effects were recorded only when there was an unambiguous description in the medical records of benefit or adverse effect. An adverse effect-benefit ratio was used as a descriptive marker of risk versus benefit, defined as the number of patients who had an adverse effect divided by the number of patients who had a benefit, for each medication. Adverse effects were graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf [accessed in May 2015]). The doses of each medication used were compared to maximum doses recommended in the Australian monthly index of medical specialties formulary (available at http://www.mimsonline.com.au), the Children's Hospital at Westmead 'in hospital' medication guidelines, and the paediatric drug formulary from the Royal Children's Hospital, Melbourne (available at http://www.rch.org.au/clinicalguide/forms/drugDoses.cfm).

Modified Rankin scores[9] were used to grade disease severity at admission, during hospital stay, at discharge, and at last available follow-up. Medical and nursing progress notes were used to ascribe modified Rankin scores at different stages of the illness. Independent sample Student's *t*-test, $\chi^2$ test, or Mann–Whitney *U* test were used to compare different patient groups or other variables. Pearson's two-tailed correlation and Spearman's rank correlation were applied to examine correlation between number of medications used and other parameters.

**What this paper adds**

- First descriptive study of symptomatic treatment in anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.
- Sedating medications are helpful for management of multiple symptoms.
- Antipsychotic-related adverse effects may outweigh their benefit in anti-NMDAR encephalitis.

## RESULTS

### Demographics

The demographic parameters of the cohort are described in Table II. Sixteen patients were identified from Australia and 11 patients from New Zealand. These included 12 male and 15 female patients. One adolescent female from New Zealand had an ovarian teratoma. The mean age at admission was 7 years 1 month (range 1y 1mo–14y 11mo). The mean duration of admission was 69 days (range 10–224d; median 62d). Forty-eight per cent of patients (13/27) needed intensive care with a mean stay of 23 days (range 1–44d). Of the 27 patients, 16 were from the Pacific Islands, and more patients in New Zealand (10/11) were Pacific Islanders compared to Australia (six/16) ($\chi^2$=6.9, df=1, $p$<0.05). All patients were followed up for 1 year or longer, except four patients treated in the year preceding this study and one patient who was lost to follow-up (Table II). The mean duration of follow-up was 3 years 6 months (range 2mo–12y 4mo, median 2y 8mo). Of the 27 patients, 15 had made a near complete recovery at the time of the last follow-up (modified Rankin scores 0 or 1), whereas three out of 27 patients, all Pacific Islanders, were left with moderate to severe disability (modified Rankin scores ≥4 at mean 3y follow-up).

### Immune therapy

Twenty-three patients received first-line immune therapy during their first admission including intravenous immunoglobulin, intravenous methylprednisolone (IVMP), plasma exchange, and oral prednisolone. Of the 14 patients diagnosed retrospectively (admitted before 2007), 10 were empirically treated with first-line immune therapy. First-line agents were started at a median of 13 days after disease onset in prospectively diagnosed patients (mean 20d, range 4–46d) while they were first used at a median of 21 days (mean 56d, range 8–363d) after disease onset in patients who were not prospectively diagnosed.

Eighteen patients received intravenous immunoglobulin at a dose of 2g/kg given over 2 to 5 days, of whom 14 were given a further two to six doses at monthly intervals. Seventeen patients were given IVMP at a dose of 30mg/kg/day over 3 to 6 days. Two of these seventeen were given repeat monthly IVMP for up to 3 months. Fourteen out of seventeen patients who received IVMP were given a tapering dose of oral prednisolone starting at a dose of 1 to 2mg/kg/day and tapered over 2 to 10 months. Seven patients underwent five or six cycles of double-volume plasma exchange over 5 to 12 days.

Eight patients received a second-line agent (rituximab *n*=seven; cyclophosphamide *n*=two; azathioprine *n*=one).

**Table I:** Details of different categories of medications used with number of patients, duration of use, breakdown of different indications for use, perceived benefit (%), and adverse effects (AE)

| | | | Indication | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Medication category | Medication | *n* | Agitation | Movement disorder | Seizures | Psychosis and mood disturbance | Sleep disturbance | Median duration of use (mean; range) in days | Benefit % (*n*) | Adverse events-benefit | AE type (CTCAE grade) |
| Benzodiazepines (*n*=25) | Midazolam | 23 | 13 | 5 | 12 | | | 12 (27; 1–117) | 91 (21/23) | 0.04 (1/23) | Respiratory depression (-) |
| | Diazepam | 15 | 11 | 2 | 1 | 1 | 1 | 27 (40; 1–163) | 73 (11/15) | 0.18 (2/15) | Respiratory depression (-)<br>Sedation (3) |
| | Lorazepam | 10 | 10 | 3 | 1 | | | 31 (61; 1–204) | 60 (6/10) | 0 | |
| | Clobazam | 7 | 4 | 4 | 2 | | 2 | 23 (49; 12–134) | 42 (3/7) | 0.67 (2/7) | Sialorrhoea (2)<br>Sedation (2) |
| | Clonazepam | 3 | 1 | 3 | | | | 3 (9; 1–24) | 67 (2/3) | 0 | |
| Anticonvulsants (*n*=25) | Phenobarbital | 17 | 10 | 3 | 10 | | | 50 (63; 1–210) | 59 (10/17) | 0.10 (1/17) | Seizure on rapid withdrawal (2) |
| | Sodium valproate | 14 | | 6 | 11 | 1 | | 120 (184; 1–867) | 57 (8/14) | 0.38 (3/14) | Agitation (3,2)<br>Thrombocytopenia (2) |
| | Phenytoin | 12 | | | 12 | | | 10 (13; 1–28) | 58 (7/12) | 0.14 (1/12) | Agitation (3) |
| | Levetiracetam | 9 | | | 9 | | | 56 (217; 3–892) | 33 (3/9) | 0.33 (1/9) | Sedation (2) |
| | Carbamazepine | 7 | | 4 | 4 | | | 90 (139; 2–410) | 57 (4/7) | 0 | |
| | Topiramate | 2 | | | 2 | | | 2 (2; 1–3) | 0 | – | |
| | Lamotrigine | 1 | | | 1 | | | 4 | 0 | – | |
| Sedatives and sleep medications (*n*=23) | Chloral hydrate | 20 | 20 | 1 | | | 2 | 44 (70; 1–381) | 60 (12/20) | 0.2 (2/20) | Respiratory depression (-)<br>Sedation (3) |
| | Clonidine | 15 | 13 | 7 | | 1 | 4 | 79 (75; 7–222) | 80 (12/15) | 0 | |
| | Melatonin | 13 | | | | | 13 | 94 (167; 11–886) | 54 (7/13) | 0.14 (1/13) | Agitation (3) |
| | Ketamine | 6 | 5 | 1 | | | | 5 (8; 1–19) | 100 (6/6) | 0 | |
| | Trimeprazine | 5 | 3 | 3 | | | | 5 (19;1–69) | 100 (5/5) | 0 | |
| | Dexmedetomidine | 2 | 2 | | | | | 5 (5; 4–6) | 100 (2/2) | 0 | |
| | Zopiclone | 2 | | | | | 2 | 35 (35;32–39) | 50 (1/2) | 0 | |
| | Promethazine | 1 | | | | | 1 | 1 | 0 | – | |
| Antipsychotics (*n*=12) | Risperidone | 8 | 5 | | | 5 | | 9 (15; 1–51) | 13 (1/8) | 4 (4/8) | NMS (-) Dystonic reaction (3) |
| | Haloperidol | 7 | 5 | 1 | | 2 | | 7 (7; 2–14) | 14 (1/7) | 3 (3/7) | Dystonic reaction (3,3)<br>Long QT (2) |
| | Droperidol | 2 | 2 | | | | | 7 (7; 2–12) | 50 (1/2) | 1 (1/2) | NMS (-) |
| | Thioridazine | 2 | | | | 2 | | 267 (267; 6–528) | 50 (1/2) | 0 | |
| | Olanzapine | 2 | 1 | | | 1 | | 20 (20; 4–35) | 50 (1/2) | 2 (2/2) | Agitation (2,3)<br>Dysarthria (2) |
| Medications for movement disorders (*n*=10) | Levodopa | 6 | | 6 | | | | 168 (151; 23–210) | 50 (3/6) | 0 | |
| | Benztropine (benzhexol) | 6 | | 6 | | | | 30 (34; 3–85) | 33 (2/6) | 0 | |
| | Baclofen | 3 | | 3 | | | | 25 (57; 10–136) | 0 | 1 (1/1) | Respiratory depression (4) |
| | Amantadine | 1 | | 1 | | | | 3 | 0 | – | |
| | Bromocriptine | 1 | | 1 | | | | 22 | 100 (1/1) | 0 | |

CTCAE, Common Terminology Criteria for Adverse Events (Grades according to CTCAE v4.0.Each number represents one patient; - indicates that a grade is not available for that category); NMS, neuroleptic malignant syndrome.

**Table II:** Demographic description of children with anti-*N*-methyl-D-aspartate receptor encephalitis of Pacific Islander origin and other racial groups from Australia and New Zealand

| Patients | Mean age at presentation (range) in years and months | Sex | Prospectively diagnosed | Mean duration of admission (median; range) in days | Mean PICU stay in days (*n*=admitted to PICU) | Mean number of symptomatic medications per patient (range) | Treated with immune therapy | Mean follow-up (median; range) in years and months | Mean mRS admission/ discharge/ last follow-up |
|---|---|---|---|---|---|---|---|---|---|
| Other racial groups | | | | | | | | | |
| Asian (*n*=6) | 6y 4mo (1y 1mo–12y 7mo) | M=5 F=6 | 5/11 | 96 (82; 18–224) | 6 (*n*=5/11) | 8 (1–14) | 9/11 | 4y 2mo (4y 5mo; 5mo–11y 4mo) | 3.5/2.6/1.2 |
| South Asian (*n*=2) | | | | | | | | | |
| Middle Eastern (*n*=1) | | | | | | | | | |
| White (*n*=2) | | | | | | | | | |
| Pacific Islanders[a] | | | | | | | | | |
| Kanak(*n*=4)[b] | 7y 7mo (1y 6mo–14y 11mo) | M=7 F=9 | 8/16 | 65 (59; 10–163) | 15[c] (*n*=8/16) | 8 (1–16) | 14/16 | 3y 3mo (2y 1mo; 2mo–12y 4mo) | 3.6/3.2/1.8 |
| Wallisian (*n*=2)[b] | | | | | | | | | |
| Maori (*n*=6) | | | | | | | | | |
| Samoan (*n*=4) | | | | | | | | | |

[a]Includes New Zealand Maori. [b]Australia site. [c]$p<0.05$ on comparing means. PICU, paediatric intensive care unit; mRS, modified Rank score; M, male; F, female.

All seven patients who received rituximab were given four weekly doses of 375mg/m$^2$/dose. Immune therapy was generally well tolerated; however, one patient was noted to have osteopenia leading to a femoral fracture after repeated monthly high-dose IVMP, one patient had an intravenous catheter site bleed, and another had an anaphylactic reaction to cryoprecipitate during plasma exchange.

### Symptomatic medications

A total of 33 different medications were used for symptomatic treatment (Tables I and SI) with a mean of eight medications used per patient. Even though 14 patients were retrospectively diagnosed, they received a similar number of symptomatic medications (mean 8) to those prospectively diagnosed (mean 7). The number of medications used for symptomatic treatment correlated significantly with the duration of admission ($r$=0.755, $p$<0.001) and with the duration of intensive care unit stay ($r$=0.583, $p$<0.005). However, they did not correlate with disease severity at any stage of the illness. There was no significant difference in the number of medications used in those who presented early within a week of disease onset (mean 8, median 6) and those who presented later (mean 10, median 8).

The symptoms treated were agitation (*n*=25), seizures (*n*=24), movement disorders (*n*=23; specifically, stereotypy, *n*=17; chorea, *n*=10; dystonia, *n*=nine; akinesia, *n*=one; catatonia, *n*=three), sleep disruption (*n*=17), psychiatric symptoms (*n*=10), and dysautonomia (*n*=four). Sleep disorders were treated in more retrospectively diagnosed patients (12/14, $\chi^2$=6.5, df=1, $p$<0.05) compared to prospectively diagnosed patients (five/13). Likewise, seizures were treated in 13 out of 14 retrospectively diagnosed patients compared to seven out of 13 prospectively diagnosed patients ($\chi^2$=5.3, df=1, $p$<0.05). All other symptoms were treated in similar proportions of patients in these groups. The medications used included five different benzodiazepines (*n*=25), seven anticonvulsants (*n*=25), eight sedatives and sleep medications (*n*=23), five antipsychotics (*n*=12), and five medications for movement disorders (*n*=10) (Tables I and SI). The more commonly used medications are depicted in Figure 1 with benefit and adverse effects. Different categories of medications were used in similar proportions of prospectively and retrospectively diagnosed patients, except medications for movement disorders that were used more commonly in retrospectively diagnosed patients (eight/14) compared to prospectively diagnosed patients (two/13, $\chi^2$=5.0, df=1, $p$<0.05).

The benzodiazepines used included midazolam (*n*=23), diazepam (*n*=15), lorazepam (*n*=10), clobazam (*n*=seven), and clonazepam (*n*=three). These were used for indications of agitation, seizures, movement disorders, sleep disturbance, and mood stabilization as listed in Table I. The total daily doses were within recommended limits, except for diazepam which was used in supra-maximal doses (up to seven times the daily upper limit of normal) in 10 patients. Midazolam, used as intravenous infusion, intravenous bolus, or buccal dose, had the highest benefit of 91.3%. Intravenous midazolam used in the intensive care

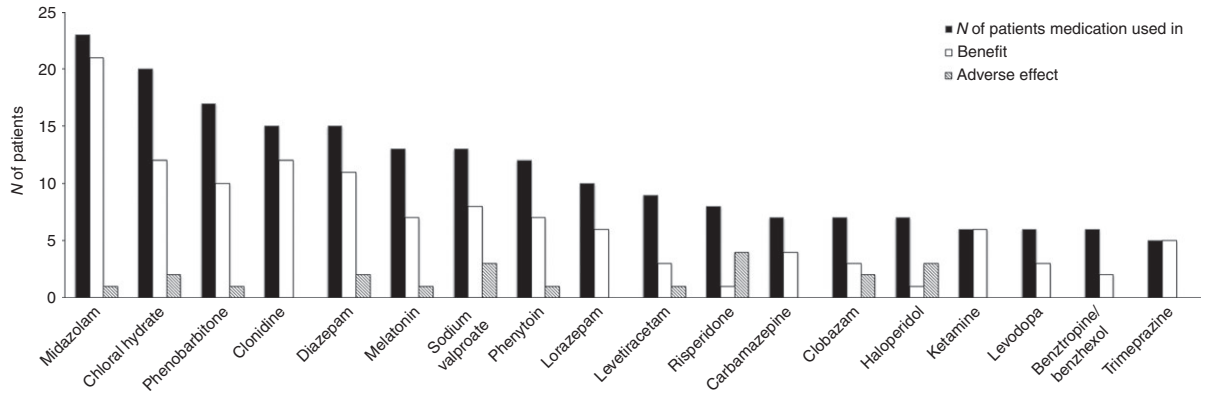


**Figure 1:** Medications used in five or more patients (number of patients – medication used in, benefit seen, adverse effect seen).

setting was often weaned slowly on the wards and switched to buccal 'as required' doses. Despite the use of other concomitant sedative medications, benzodiazepines were generally well tolerated with adverse effects noted in only 4 out of 27 patients (see Table I for details and Common Terminology Criteria for Adverse Events grades). These adverse effects included excessive sedation, respiratory depression, and sialorrhoea, and did not lead to discontinuation of the medication in any patient.

Seven different anticonvulsants (in addition to benzodiazepines) were used for acute and ongoing management of definite or suspected seizures. These included phenobarbital (*n*=17), sodium valproate (*n*=14), phenytoin (*n*=12), levetiracetam (*n*=nine), carbamazepine (*n*=seven), topiramate (*n*=two), and lamotrigine (*n*=one). Phenobarbital, sodium valproate, and carbamazepine were also used to manage movement disorders in some patients (Tables I and SI). In addition, phenobarbital was used for management of agitation in 10 patients and sodium valproate was used as a mood stabilizer in one patient. The perceived benefit of different anticonvulsants was similar, other than lamotrigine and topiramate (Table I). Adverse events to anticonvulsants were noted in five out of 27 patients, which included worsening agitation, thrombocytopenia, excessive sedation, and seizure on rapid withdrawal (Table I). These events resulted in dose adjustment of the respective medications but did not lead to their discontinuation in any patient.

Sedative and sleep medications other than benzodiazepines (eight different medications) had a noted mean benefit of 67.4% per medication. These included chloral hydrate (*n*=20), clonidine (*n*=15), melatonin (*n*=13), ketamine (*n*=six), trimeprazine (*n*=five), dexmedetomidine (*n*=two), zopiclone (*n*=two), and promethazine (*n*=one). These medications were well tolerated with a mean adverse effect:benefit of 0.04 per medication. Oral clonidine was useful for managing agitation, stereotypical movements, and sleep disturbance, and intravenous clonidine was a safe and useful option in the intensive care unit setting.

Five different antipsychotics were used in 12 patients for management of psychosis and/or agitation. These included risperidone (*n*=eight), haloperidol (*n*=seven), droperidol (*n*=two), thioridazine (*n*=two), and olanzapine (*n*=two). Haloperidol was used at a high dose of 20mg/day (the usual maximum adult dose is 15mg/day) in one adolescent. Antipsychotics had the lowest mean benefit per medication of 25.3% and an adverse effect-benefit ratio of 1.6 per medication. Adverse events were noted in seven out of 12 patients treated with antipsychotics, and included dystonic reaction (*n*=three with haloperidol and risperidone), neuroleptic malignant syndrome (*n*=three with risperidone and droperidol), prolonged QT interval (*n*=one with haloperidol), worsening agitation (*n*=one with olanzapine), and dysarthria (*n*=one with olanzapine). The adverse effects led to discontinuation of the respective medication and restricted the median duration of use of antipsychotics to only 9 days. In all cases discontinuation of the antipsychotic agent led to reversal of the adverse symptoms.

In addition to the use of some benzodiazepines and anticonvulsants for movement disorders, five medications were used specifically for movement disorders. These included levodopa-carbidopa (*n*=six), central anticholinergics (benztropine *n*=five; benzhexol *n*=one), oral baclofen (*n*=three), amantadine (*n*=one), and bromocriptine (*n*=one) (Table I). The mean benefit was only 35% per medication. Respiratory depression was noted with baclofen in one patient who was also receiving benzodiazepines and other sedatives. This resolved on discontinuation of baclofen.

Manifestations of dysautonomia were noted in 20 out of 27 patients. Unexplained fever was treated with antipyretics in 17 out of 27 patients, hypertension in two patients was treated with nifedipine and clonidine, hypersalivation in two patients was treated with glycopyrrolate and hyoscine patches, and recurrent bradycardia and asystole in one patient was treated with atropine and isoprenaline infusion. Features of dysautonomia seen in six other patients (bradycardia, lability of blood pressure) did not require treatment.

## DISCUSSION

Our cohort demonstrates the challenges faced in the management of children with anti-NMDAR encephalitis. The

patients had a mean admission of 2 months, half of the patients required treatment in intensive care units, and the majority of patients were given multiple medications to manage a broad variety of symptoms. After a mean follow-up of 3 years 7 months, 15 out of 27 (55%) patients had made a good recovery (eight/14 patients retrospectively diagnosed, seven/13 patients prospectively diagnosed), whereas the remaining 12 patients were left with a range of disability (although prolonging follow-up may have improved reported outcomes). In a recent large case series, approximately 75% patients were noted to make a complete recovery at 2-year follow-up, and the mortality has now fallen from 25% when this condition was initially described to approximately 7%.[1,10] Pacific Islanders made up nearly 60% of our cohort, and the three patients with the poorest outcome were from this group. This over-representation of Pacific Islanders compared to other racial groups is similar to the demographic representation among non-whites noted in other series.[11] This may suggest a vulnerability to disease, which could be genetically derived.

Despite improvement in long-term outcomes, symptomatic management of patients during their protracted acute illness remains a challenge for clinicians, nursing staff, and families. In our series, we did not observe a dramatic effect with any symptomatic medication, and the benefit was only partial for many drugs. Medications were commonly used for more than one indication and sometimes benefit was noted for one symptom and not others. However, the retrospective nature of the study and overlap between symptoms such as stereotypical hyperkinetic movements and agitation made it difficult to separate symptom-wise benefits individually. This study was limited by the reliance on subjective measures of benefit, but is the first such report to describe symptomatic management in detail.

Behavioural symptoms, particularly agitation, are commonly seen in children with anti-NMDAR encephalitis. Agitation was treated in 93% of patients and was often the most distressing symptom for parents. Agitated behaviour may be intermittent at first, becoming more frequent in the florid stage of the illness. This agitated state has been likened to status dissociatus[12] and the dissociative state seen with ketamine anaesthesia.[13] Agitation is thought to be caused by disruption of the frontal lobe inhibition of thalamic–brainstem centres.[14] In our cohort, sedative medications were used to treat agitation with some benefit (Table I). Midazolam, diazepam, chloral hydrate, and clonidine were widely used with a good adverse effect-benefit ratio (0.04–0.2). Phenobarbital[15] (benefit in 10/17 patients) and ketamine (benefit in six/six patients) are antagonists of the NMDAR. Both these medications were effective in suppressing agitation in our cohort, and no symptomatic worsening was noted despite their effect on the NMDAR. One previous report has described a dramatic sustained benefit with ketamine,[16] whereas others have not found it to be useful.[6] Other candidate medications that act on the NMDAR (e.g. dextromethorphan and memantine) have been postulated to be useful for the symptomatic management of anti-NMDAR encephalitis, although their clinical use is limited.[17,18]

Sleep disorders are common in anti-NMDAR encephalitis and in other autoimmune encephalopathies.[19] Improved sleep is important in the management of this and other movement disorders, and is hypothesized to improve neurological recovery.[20] Clonidine was often initiated early for sleep disturbance with an aim to eventually restrict it to a night-time dose, along with early use of melatonin. We did not have any concerns with rebound hypertension with the use of clonidine in this cohort of patients, although blood pressure monitoring is recommended especially when clonidine is stopped after short use (Table III). For sleep induction, we also used sedative medications including benzodiazepines starting with an intermediate–long-acting benzodiazepine such as clobazam or lorazepam, supplemented by buccal midazolam or chloral hydrate when needed. Similar to clonidine, the dosing of sedative medications was shifted towards evening/night-time doses as patients tolerated weaning to smaller doses, to try and maintain a sleep–wake diurnal cycle. We are also mindful of the use of environmental measures such as ambient lighting and timing of physical interventions like physiotherapy and play therapy during daylight hours to assist in correction of the sleep–wake cycle.

Movement disorders are noted in the majority of children with anti-NMDAR encephalitis and were treated in 85% of our series. The movements are often hyperkinetic and stereotyped with perseverative components, as recently described.[21] Symptomatic treatment is often initiated to facilitate patient care, and to avoid the risks of injury and rhabdomyolysis, in addition to reducing patient and parental distress. Sedative medications such as benzodiazepines and some anticonvulsants appeared to be beneficial in managing movement disorders in our cohort, and were similar to the drugs used to treat agitation. 'Conventional' movement disorder medications such as levodopa and central anticholinergics had a more modest benefit. This is possibly because the origin of abnormal movements in anti-NMDAR encephalitis is not purely caused by a basal-ganglia dysfunction involving dopaminergic pathways. We tend to use these medications infrequently now as reflected by the decreasing use in prospectively diagnosed patients in this cohort. Our current approach is to choose medications that have a broad effect on multiple symptoms if possible. Hence, we increasingly rely on long-acting benzodiazepines, sedatives such as clonidine, and anticonvulsants such as phenobarbital or sodium valproate to try to improve abnormal movements or stabilize mood. Lorazepam is helpful in the treatment of catatonia, and electroconvulsive therapy has been successfully used to treat catatonia in anti-NMDAR encephalitis, although we did not use electroconvulsive therapy in our cohort.[22,23]

The management of psychiatric symptoms was more challenging. While sedative medications again helped manage aggression and mood lability, the use of antipsychotic medications was less efficacious and was associated with adverse

**Table III:** Suggested practice points for selected medications used in anti-*N*-methyl-D-aspartate receptor encephalitis (doses used as per local guidelines)

| Medication group | Indications | Monitoring | Comment |
|---|---|---|---|
| IVMP | First-line immune suppression | Blood pressure, blood glucose | AE due to IVMP such as agitation, psychosis, and hypertension may be difficult to separate from disease manifestations |
| IVIG | First-line immune suppression | Monitor for dysautonomia, allergic reactions, and signs of aseptic meningitis | If AE occur, a slower rate or infusion can be used. Premedication with antihistaminic agents can minimize allergic reactions |
| Plasmapheresis | First-line immune suppression | Therapeutic drug levels of anticonvulsants | AE related to medication withdrawal may occur |
| Benzodiazepines | | | |
| Midazolam | Agitation<br>Stereotypies<br>Sleep disorders | Monitor for respiratory depression with concomitant sedative use | Buccal or intranasal doses are good rescue options for periods of agitation or intractable stereotypies and seizures but intravenous infusion may be needed |
| Other benzodiazepines | Agitation<br>Seizures<br>Stereotypies<br>Catatonia<br>Sleep disorders | Monitor for respiratory depression with concomitant sedative use | Consider use of lorazepam for perseverative symptoms and other features of catatonia<br>Substitute infusions for oral doses and taper to avoid withdrawal symptoms |
| Anticonvulsants | | | |
| Phenobarbital | Agitation<br>Seizures<br>Movement disorders | Supra-therapeutic drug levels may sometimes be tolerated if benefit seen and respiratory status is not compromised | Taper doses when stopping |
| Sodium valproate | Agitation<br>Seizures<br>Chorea<br>Psychiatric symptoms | Monitor blood counts and liver function | Useful for multiple symptoms, particularly for mood stabilization |
| Levetiracetam | Seizures<br>Movement disorders | | Behavioural worsening and agitation may occur and may be difficult to separate from disease symptoms |
| Topiramate | Seizures | | Speech regression, mood disturbance, and mutism are known AE and may be difficult to separate from disease symptoms |
| Sedative and sleep medications | | | |
| Chloral hydrate | Agitations<br>Stereotypies<br>Sleep disorder | Monitor for cumulative sedation with other agents | Safe with multiple doses in our experience. Useful for PRN use. Paradoxical agitation may occur in some cases |
| Clonidine | Agitation<br>Sleep disorder<br>Stereotypies | Blood pressure for hypotension at low doses and rebound hypertension when stopping<br>Monitor for excessive sedation | Hypotension is a concern at low doses<br>Can be used 2–3 hourly as oral doses, infusion can be used |
| Ketamine | Agitation, stereotypies | Monitor for cumulative sedation and respiratory depression | Insufficient data for use outside ICU setting<br>No AE noted with infusions |
| Melatonin | Sleep disorder | | Sleep induction is supported by timing doses of sedative medications with melatonin |
| Dexmedetomidine | Agitation<br>Movement disorder<br>Sleep disorder | Monitor for cumulative sedation with other agents | Mechanism of action is similar to clonidine and is more expensive |
| Antipsychotics | | | |
| Risperidone<br>Haloperidol<br>Thioridazine<br>Olanzapine<br>Droperidol | Psychiatric symptoms<br>Agitation | Monitor for extrapyramidal AE, QT prolongation<br>Cardiovascular AE with long-term use | High rate of AE<br>Consider use of anticonvulsants or more selective antipsychotics at low starting doses |
| Atypical antipsychotics – Quetiapine, Aripiprazole | Psychiatric symptoms<br>Agitation | Monitor for extrapyramidal AE, QT prolongation<br>Cardiovascular AE with long-term use | Risk of NMS and Tardive dyskinesia<br>Long-term safety/outcome data is not available |
| Medications for movement disorders | | | |
| Levodopa | Dystonia | | Dopamine responsiveness of dystonia is unclear in this setting |
| Anticholinergics | Dystonia (disease or drug-related) | | Agitation, gut hypomotility as AE may be difficult to separate from disease symptoms |
| Baclofen | Dystonia<br>Movement disorders | Respiratory depression | Hypotonia and respiratory depression. Limited benefit – preferably avoid |

AE, adverse effect; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; PRN, pro re nata (as required); ICU, intensive care unit; NMS, neuroleptic malignant syndrome.

events. In this series antipsychotic use was associated with dystonic reaction or neuroleptic malignant syndrome in 58% patients treated, and these side effects improved on discontinuation of the medication. Previous reports[24–26] have also noted this predisposition to antipsychotic-related adverse events in anti-NMDAR encephalitis. These observations suggest a higher vulnerability to antipsychotic-related adverse effects in children with anti-NMDAR than the previously reported 14% to 18% incidence in children treated for delirium or other indications.[27] Patients with Sydenham chorea also appear to have a vulnerability to antipsychotic-induced adverse events with drug-related parkinsonism seen in 5.5% of patients in one series.[28] We hypothesize that agents such as quetiapine with less dopamine-2 receptor blockade may be better tolerated. In our practice we initiated antipsychotics cautiously, and have tried to use very low starting doses with gradual titration (Table III).

Seizures are seen in the acute stage of anti-NMDAR encephalitis and remit in most cases within a few months.[1,29] In our series, rescue medications for seizures were not required after the first month of illness. Some patients ($n$=7) were empirically given anticonvulsants without proven seizures. While maintenance anticonvulsants were sometimes continued for 2 years or longer, it is possible that these medications could be weaned earlier to reduce potential side effects. No anticonvulsant had a clear advantage, and we have chosen agents that may help other symptoms such as agitation, stereotypies, or mood disturbance (phenobarbital, sodium valproate, and longer-acting benzodiazepines).

It is important to recognize and treat dysautonomia when present. Cardiac rhythm disturbances, asystole (as seen in one patient), and lability of blood pressure can all be life-threatening. Sometimes these symptoms, particularly changes in heart rate and blood pressure, can be exacerbated with the use of high-dose steroids and intravenous immunoglobulin.[30]

The physiological explanation for many symptoms seen in anti-NMDAR encephalitis and consequently the mechanism by which certain medications help, remains unresolved. There is clear evidence of NMDAR hypofunction resulting from the antibodies in in vitro studies; however, the effect on other neurotransmitters and receptors is not clear. Immune therapy is the mainstay of treatment and early escalation to second-line agents is key to early and complete recovery when symptoms do not improve in the first few weeks of illness. Although this study focused on pharmacological measures, the role of parental involvement and support, nursing care, and rehabilitative and allied health input cannot be overstated.

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## SUPPORTING INFORMATION

The following additional material may be found online:

**Table SI**: Individual patient details of immune therapy and symptomatic medication use during first presentation with anti-NMDAR encephalitis

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