

### Synergetic Effect of Electroconvulsive Therapy and Clozapine Therapy in Treating Severe Intractable Aggressive Behaviour in an Adult with Intellectual Disability: A Case Report

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#### ABSTRACT

There is scarce literature on the use of either clozapine or Electroconvulsive therapy (ECT) and/or their combination in patients having intellectual disability with aggression. To the best of our knowledge, we report the first case of combination use of ECT and clozapine in treating severe intractable aggressive behaviour in a 19-year-old male of Chinese descent with severe intellectual disability. Patient presented with disturbed sleep pattern, self-injurious, and severe aggressive behaviour soon after the announcement of Movement Control Order (MCO) by the government of Malaysia sometime in March 2020 as preventive measure to contain COVID-19 spread. Consequently, patient's daily routine was affected, and he had to stay home. Psychosocial interventions were attempted by family members. However, the challenging behaviour persisted for 3 months which led to caregiver burnout and subsequent admission. During the hospitalisation, occupational therapy was initiated, and medication treatment was optimised. Blood parameters investigation was unremarkable. The aggressive behaviours were assessed using modified overt aggression scale (MOAS) and brief psychiatry rating scale (BPRS). There was no satisfactory improvement noted despite being on three second-generation antipsychotics (Olanzapine, Quetiapine and Amisulpride). Later, concurrent use of clozapine and ECT were initiated. Patient's improvement was satisfactory, and he was discharged with Clozapine at 200mg daily as well as after completing 14 sessions of bitemporal ECT (Thymatron system IV, Illinois, USA), thrice a week with 0.5 millisecond pulse width, 70Hz and titration between 25-508 milliCoulombs (mC). The combination use of ECT with clozapine appeared to have a both synergetic and efficacious effects in treating intellectual disability with aggressive behaviours.

**KEYWORDS:** Clozapine, Electroconvulsive Therapy, Intellectual Disability, Aggressive behaviour

#### INTRODUCTION

Challenging behaviours that frequently related to patients with intellectual disabilities (ID) included agitated and aggressive behaviour, sleep disturbance as well as self-injury behaviour. Such behaviours have been demonstrated to occur almost daily and may endanger physical safety of the patient and/or others. Often it led to caregiver burnout yet not seeking help as believing that it is due to the disability and cannot be treated [1]. Unfortunately, when the patient is brought to health care professional, such behavioural problems may be attributed to be part of their disability without exploring for the presence of other symptoms related to physical illness.

Thus, it is essential to manage the challenging behaviours promptly as well as effectively and thereby preventing caregiver burnout or diagnostic overshadowing. Aggressive and challenging behaviours include physically aggressive behaviour, verbally aggressive behaviour and destructive behaviour. These has been reported in one among four patients with intellectual disability [2]. The paucity of studies in the usage of psychotropics particularly clozapine and/or electroconvulsive therapy (ECT) in this population may further discourage both patients and health professionals for its consideration. We present a successful management of severe intractable aggressive



behaviours in an adult with intellectual disability via synergetic effect of combining clozapine with ECT.

## CASE PRESENTATION

A 19-year-old male of Chinese descent with severe ID which was diagnosed when he was 11-year-old using Comprehensive Test of Nonverbal Intelligence (CTONi). Its subtests scores were as follows: nonverbal intelligence quotients (IQ) = 64 (very poor), pictorial nonverbal IQ = 59 (very poor) and geometric IQ = 74 (very poor) which were equivalent to that of a child aged 6 years up to 8 years 11 months.

With regards to history, the antenatal and postnatal histories were unremarkable. Genetic testing was not done as patient has no syndromic facies to suggest any genetic abnormality condition clinically. He has no other comorbid physical illness and no family history of ID or psychotic illness.

He was living in Selangor with his family who consisted of father, mother, and 2 younger siblings. Patient had been regularly attending a rehabilitation centre on every Tuesday, Friday and Saturday. At the centre, he had interactive activities such as drawing, handcraft, gaming, and cooking. During other days, he would follow his mother to her workplace which was a hair salon. He would spend time from 9am till 5pm at a designated space to play with his mobile gadget.

He presented with challenging behaviours which was characterised by disturbed sleep pattern (slept for an of average 3 hours per day), self-injurious and aggressive behaviours. He was physically aggressive (fighting with family members), verbally aggressive (shouting and being provocative towards family members) and had destructive behaviour (throwing objects and breaking up furniture). Otherwise, there was no recent adverse life events, no mood disorder symptoms, substance usage or any known neurological disorder. He was evaluated for post-traumatic stress disorder (PTSD) symptoms to exclude recent traumatic event but did not fulfil the criteria. These symptoms started during March 2020 soon after the movement control order (MCO) which was announced in Malaysia as preventive measure of COVID-19 spread. As a result, patient's daily routine was disturbed, and he had to stay home. The onset of

the episode was gradual but worsening for the past 2 months and family members had difficulty to take care of patient activities of daily living as well as personal safety.

Prior to admission, family attempted to engage patient with home activities such as doing house chores, watching movie and gaming. However, family could not manage patient's behaviour as he was constantly being irritable and physically aggressive towards family. These behaviours lasted for over 3 months prior to admission. Formal behavioural analysis was not carried out due to limited resource. The assessment was done based on clinical judgement. Medication treatment was simultaneously carried out. Sodium valproate and olanzapine were prescribed for impulsivity and acute control of aggressive behavioural disturbance respectively. He was compliant to medications but there was no satisfactory improvement with sodium valproate up to 1gram per day in combination with olanzapine up to 20mg for more than 3 months. He was admitted to a tertiary inpatient unit following an episode of self-harm behaviour. During admission, his body mass index (BMI) was 25.2kg/m<sup>2</sup> (body weight 80kg and height 1.78m). Clinical examination revealed mild strabismus and scoliosis. Blood investigations showed normal complete blood count (CBC) and differentials, serum urea, electrolytes, creatinine, calcium, phosphate, and magnesium. His therapeutic drug monitoring for valproic acid at 1g was 605.0umol/L, which was within therapeutic range. His liver function test showed increased alanine aminotransferase at 162u/l and aspartate transferase at 117u/l with other liver parameters being normal.

Upon admission, he was assessed with modified overt aggression scale (MOAS) (score of 30) and brief psychiatry rating scale (BPRS) (score of 72). Olanzapine and sodium valproate were titrated down in view of his deranged liver enzymes. He was started on tablet Quetiapine intermediate released (IR) as main treatment with short duration of chlorpromazine for sedative purpose in the acute phase of stabilisation. He required intramuscular zuclopenthixol acetate 75mg on 4 occasions for control of his aggressive behaviour. There was no satisfactory improvement with Quetiapine up to 1g at 4<sup>th</sup> week of admission. The MOAS was 23 and BPRS was 54. There was a trial of home leave to

encourage reintegration and rehearse of social and environment. However, patient was brought back to ward on the second day due to unmanageable aggressive behaviours. Quetiapine IR was then cross tapered with amisulpride in view of no response noted. Amisulpride was prescribed till 1g at 6<sup>th</sup> weeks of admission but there was no satisfactory response. Since patient's symptoms did not improve, a course of electroconvulsive therapy (ECT) was initiated. He was treated with bitemporal ECT (Thymatron system IV, Illinois, USA), thrice a week with 0.5 millisecond pulse width, 70Hz and titration from 25-403 milliCoulombs (mC). Incidentally, the occupational therapist was unable to get patient to participate in activities, such as gaming, colouring and exercises. Discussion was made with family members for clozapine initiation. The clozapine titration had adhered to the clozapine treatment guidelines (3). Patient's challenging behaviours started to show improvement at clozapine

37.5mg daily with thrice weekly ECT. His MAOS score was 15 and BPRS score was 29. His aggression behaviours were subsequently manageable and achieve remission at day 16 of clozapine treatment of 200mg daily as well as completing 14 sessions of bitemporal ECT (Thymatron system IV, Illinois, USA), thrice a week with 0.5 millisecond pulse width, 70Hz and titration between 25-508 milliCoulombs (mC). Patient's MOAS was 0 and BPRS was 18 upon discharge. He was planned for monotherapy treatment with clozapine and amisulpride was subsequently tapered off.

Side effects was experienced in the form of mild hypersalivation and sinus tachycardia (103-133 rate /min) with no other abnormalities on ECG. There were no other side effects noted. Test for myocarditis (C-reactive protein) and weekly complete blood counts were within normal limits. Currently, patient is in remission. He has been maintaining well with the clozapine 300mg daily and propranolol 20mg daily with vocational rehabilitation program. His MOAS score at 6<sup>th</sup> months were 0 with BPRS scored 18 (Table 1).

**Table 1** Modified Overt Aggression Scale (MOAS) and Brief Psychiatric Rating Scale (BPRS) scores according to duration of admission with date and treatment.

Week	Treatment	MOAS	BPRS
0	Olanzapine 20mg	30	72
Admission (21/6/2020)	Sodium Valproate 1g		
4	Quetiapine IR 1g	23	54
(23/7/2020)	ECT initiated		
6	Amisulpride 1g	23	44
(4/8/2020)	ECT 6 <sup>th</sup> session		
6	Clozapine 37.5mg	15	29
(8/8/2020)	ECT 8 <sup>th</sup> session		
7 Discharge	Clozapine 200mg	0	18
(21/8/2020)	ECT 14 <sup>th</sup> session		
18 Clinic	Clozapine 300mg	0	18
(7/12/2020)	Amisulpride 200mg		
23 Clinic	Clozapine 300mg	0	18
(4/1/2021)			

IR: intermediate released; ECT: electroconvulsive therapy

## DISCUSSION

The limited data especially randomised controlled trial for treatment of challenging behaviour in intellectual disability patient had indeed prevented clinician in the progress of treatment and decision making. A detailed history including mental state examination and

behavioural analysis are crucial in helping with diagnosis as well as appropriate intervention. In patients in which the challenging behaviours persist despite being treated with exhaustive interventions of psychosocial and routine psychopharmacological treatments like in this case, clozapine ought to be

considered as one of the early interventions. Thus, preventing delay in treatment thereby minimizing exposure to both patient and caregiver in terms of personal safety as well as mental health functioning.

To the best of our knowledge, this is the first case report of combining Clozapine with ECT in managing aggressive behaviour in a male adult with intellectual disability. This has been indeed an effective treatment as evidenced by 50% reduction in modified overt aggression scale and brief psychotic rating scale by the first week after their initiation. He has no metabolic syndrome, seizure, constipation, cardiovascular symptoms, or blood count abnormalities to date though had mild hypersalivation and tachycardia. Given his severity of aggression upon presentation with multiple admissions in the past, the benefit of using clozapine as long-term pharmacology treatment had certainly outweighed the risks. Patient is presently on monotherapy (after discharge from index episode) medication as compared to previous medication which were a combination of mood stabiliser, antipsychotic and benzodiazepine. Certainly, the current management has induced long term remission of aggression symptoms [4].

Apart from the perspective of clinician, feedback from the caregiver of our patient was satisfactory. It reduces the need of supervision of routine activities for the patient. Caregiver reported less stress in terms of physical, emotional and financial domains. Patient was able to spend quality time with the caregiver and there was less social stigma experienced when patient was brought to public facilities.

Decision of clozapine use in this study was made based on case reports studies. As per guidelines, clozapine is indicated for treatment resistant schizophrenia.

Regrettably, the safety data on clozapine used in patient with ID was limited from published case series. Clozapine has less potent D2 antagonist but more potent on D1, D3 and D4 antagonist. It has antagonist effect on alpha 1 and alpha 2 adrenergic, muscarinic, cholinergic, H1-histaminic and serotonergic receptor. It was hypothesised that the clozapine's complex receptor-binding affinities for D2, D4 and 5-HT<sub>2A</sub> receptors as biological approach of managing impulsivity and aggression [5].

Frogley et al [5] conducted a systematic review of the anti-aggressive effects by clozapine, which included 52 studies from animal studies, randomised controlled trials, prospective non-controlled studies, retrospective studies, and case studies. It was found that clozapine's anti-aggressive effects may not only be restricted to schizophrenia but also include other non-psychotic disorders. The anti-aggressive effect of clozapine was more marked particularly in those with treatment-resistant illness and the anti-aggressive advantage was independent both of its antipsychotic and sedative effects. Buzan et al [6] reviewed the use of clozapine in 10 intellectual deficit adult cases and showed that clozapine was well tolerated and efficacious for aggression as well as self-injurious behaviour, apart from psychosis and mania in intellectual disability patients. The effectiveness did not diminish over time as the cases were treated for a duration of 13-46 months and remained in symptom control. Sajith [7] reported 3 cases of successful use of clozapine in severe intractable aggressive and self-injurious behaviours in adults with autism as well as intellectual disabilities. The total daily dose of clozapine was ranging between 400mg – 500mg per day. All three patients showed remarkable improvement with no aggressive behaviour or self-injurious behaviour elicited.

Electroconvulsive therapy (ECT) is a nonpharmacological neuronstimulation method that is often considered as last treatment when other therapies have failed and/ or when rapid reduction of severe symptoms was required [8]. Dara Gammon et al [8] reported electroconvulsive therapy has been shown to increase neuroplasticity. The other theories include the rapid release of neuroendocrine hormone. Collins et al [9] reviewed 72 case reports of ECT in patients with intellectual disability with variety of indications. Among the indications for ECT, included affective disorder, schizophrenia, behavioural disturbances, catatonia, mixed and others. Results demonstrated that ECT was effective without further cognitive deterioration. Consoli et al [10] in a retrospective study for efficacy of ECT in adolescent with ID and severe self-injurious behaviour and aggression reported a direct correlation of decreasing severe self-injurious behaviour and/or aggression with ECT therapy.

Synergistic mechanism of ECT and clozapine combination is both complex and not entirely understood. It has been postulated that via the rapid release of the effect of various neurotransmitters as well as altered permeability of blood-brain barrier which would improve the passage of clozapine and thus its efficacy.

## CONCLUSION

Challenging behaviour do occur in ID patients. Detailed history, mental state examination and behavioural analysis were important to be explored in patients with ID to avoid diagnostic overshadowing. This case report highlights its first successful management during a combination use of clozapine and ECT in treatment of severely intractable aggression behaviour in patient with ID. This would surely add support in treating challenging behaviour in ID patients using a combination of both clozapine and ECT.

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## Conflict of Interest

Authors declare none.

## Authors' contribution

Conceptualization: WDS, MAB.

Literature Review: WDS and SA.

Writing, review, editing and final approval: WDS, MAB, SA.

## List of Abbreviations

5-HT<sub>2A</sub> – 5-Hydroxytryptamine Receptor 2A

AGG - Aggression

BMI – Body Mass Index

BPRS – Brief Psychiatry Rating Scale

CBC – Complete Blood Count

COVID – 19 – Coronavirus Disease 2019

CTONi – Comprehensive Test of Nonverbal Intelligence

D1 – Dopaminergic Receptor 1

D2 – Dopaminergic Receptor 2

D3 – Dopaminergic Receptor 3

D4 – Dopaminergic Receptor 4

ECT – Electroconvulsive Therapy

H1 – Histaminic Receptor 1

ID – Intellectual Disability

IQ – Intelligence Quotient

MCO – Movement Control Order

MOAS – Modified Overt Aggression Scale

PTSD – Post-traumatic Stress Disorder

SIB – Self-injurious Behaviour

USA – United States of America

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