Key Words: viloxazine, ADHD, ASD, metabolic syndrome, enuresis

Early Positive Report of Viloxazine for a Child with Hyperkinetic Autism

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ABSTRACT *~ Herein, authors report on an ASD child with comorbid ADHD, ID, metabolic syndrome and nocturnal enuresis that failed multiple trials of psychotropic agents for behavioural dyscontrol. Viloxazine adjuventia brought about remarkable improvement spanning different domains. Purported pharmacodynamic mechanisms are briefly discussed. This case represents one of the earliest reports of viloxazine use in ASD.* Psychopharmacology Bulletin. *2025;55(1):89–92.*

Case Vignette

An 11-year-old male Qatari boy was brought in to hospital by his parents for episodic behavioural dyscontrol. He was a known case of essential Autism spectrum disorder (ASD) with mild intellectual disability (FSIQ = 62), minimally verbal, non-epileptic and currently enrolled in special schoolings. As reported, he was always hyperactive, yelling and screaming, cranky, with continuous body rocking movements and disturbed fitful sleep. He also had nocturnal enuresis that failed to respond to scheduled awakenings. He displayed escalating hetero-aggression as of late including hurling objects. He was meticulously scrutinized for potential medical and environmental causations of this behavioural decompensation but with negative yield. No behavioural interventions could be implemented due to non-engagement with high aggressivity. Our occupational therapists tried functional behavioural assessment, and diversion/distraction strategies but to no avail. Inpatient committal with structure failed to contain his

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TABLE 1

Medication Chart, Untoward Effects and Clinical Outcome of Previous Trials

Risperidone (1.5 mg/d)	5 weeks	Repeated ADRs PRL ↑ (800 U) Wt ↑ (4 Kg)
Aripiprazole (10 mg/d)	8 weeks	Ineffective PRL ↓ (250 U) Wt ↓ (1.5 Kg)
Valproate (750 mg/d)	3 weeks	Tremors LFTs ⇈ (ALT 200, AST 180) Wt ↑ (3 Kg)
Methylphenidate (2.5 mg/d)	Single Dose (1 day)	Paradoxical Agitation S. Tachycardia (HR 160 bpm)
Atomoxetine (40 mg/d)	3 months	Ineffective LFTs ↔ (ALT 50, AST 45) Wt ↓ (1 Kg)
Clonidine (300 μg/d)	2 weeks	Sleep Improved S. Bradycardia (HR 50 bpm) Hypotension (80/50) and presyncope on 2 occasions over a week
Sertraline (75 mg/d)	8 weeks	Ineffective

behavioural crisis. He has been trialled sequentially on different psychotropic medications to address behavioural facets. Medication chart, untoward effects and clinical outcome is depicted in Table 1. As such, most trials were prematurely aborted for either tolerability issues and/or lack of effectiveness. He finally showed some behavioral response, albeit mediocre, on olanzapine ODT 5 mg, over 4 weeks, including improved sleep, but at the expense of borderline metabolic syndrome (prediabetes). DSM-5-TR Attention-Deficit/Hyperactivity Disorder (ADHD) symptom profile (pronounced hyperactivity and apparent distractibility)–combined presentation, remained challenging, though. With parental informed consent, we opted for a trial of add-on viloxazine 100 mg/d to olanzapine, since other anti-ADHD agents were unhelpful. At week 3 of viloxazine trial, at dose of 200 mg/d, there was a tangible improvement in behavioural facets both clinically and objectified by marked reductions of hyperactivity (40 before treatment/15 after treatment), and irritability (35 before/16 after) subscales of Aberrant Behaviour Checklist (ABC) which was administered by a certified psychologist of our team in a single-blinded design. Behavioural response was exponentially incremental and well-maintained at W-6 and W-12 of follow-ups. No major adverse drug reactions were reported throughout the trial. Strikingly, improvement of metabolic screen (better glycemic control) and weight loss (from 49 Kg pre-treatment down to 43 Kg)

was noted and enuresis stopped altogether. We wager that case outcome reflects violxazine adjuventia to olanzapine. Parental's consent to publish this report anonymously was obtained beforehand.

Discussion

ASD is commonly associated with a host of challenging behaviours. Pharmacotherapy is indicated when psycho-social and educational interventions fail. Atypical antipsychotics have the strongest evidence-base so far, with both risperidone and aripiprazole are FDA-approved. Unfortunately, their use is fraught with cardio-metabolic and neuro-hormonal side effects and children with ASD are sorely at heightened vulnerability to these adverse effects by virtue of young age and neuro-disability[1]. Significant cohort of patients can still show no response on these agents. There is a modicum of evidence-base supporting use of olanzapine in ASD according to case reports, open-label trials and a small (n = 11) 8-week double-blind placebo-controlled trial.[2]

Empirical evidence exists for using stimulants (methylphenidate) and non-stimulants (atomoxetine, clonodine, guanfacine) to address co-morbid ADHD in ASD. Nonetheless, response is typically less robust with higher drop-out rates due to intolerability compared to neurotypical children.[3]

Viloxazine, originally marketed as a bicyclic antidepressant, and FDA-designated as an orphan drug for narcolepsy/cataplexy, was recently approved for ADHD in children aged 6-17 years at 100–400 mg/d, as a nor-epinephrine reuptake inhibitor (NRI), a non-stimulant, akin to atomoxetine. Although classified as an NRI (nor-epinephrine reuptake inhibitor), viloxazine has a composite mode of action including, inter alia, an increase of serotonin (5-HT) in PFC, 5-HT_{2C} agonism, and, 5-HT_{2B} antagonism (this mechanism is also shared by metadoxine that was previously investigated as a potential ADHD medication)–which has been demonstrated to suppress hyperlocomotion in animals, and hence the designation SNMA (serotonin-norepinephrine modulating agent) sounds more apt.[4]

Weight loss seen in this case might be ascribed to anorexogenic effects of viloxazine. Importantly, viloxazine by inhibiting CYP 1A2, to which olanzapine is a substrate, can spare higher doses (as in our case where we could stay at 5 mg/d without uptitration). And since metabolic syndrome could be dose-dependent (at least for some atypical anti-psychotics), this could be an innovative pharmacological strategy to mitigate metabolic syndrome, not unlike the previously reported use of fluvoxamine, an SSRI with CYP 1A2 inhibitor activity, to help with clozapine-related metabolic syndrome.[5]

By virtue of serotonin and norepinephrine reuptake inhibition at the presynaptic neuron in Onuf's nucleus of the sacral spinal cord, viloxazine can target nocturnal enuresis as in our report. The resultant increase in nor-epinephrine tone, stimulation of the alpha-adrenergic receptors promotes urinary continence via contraction of the bladder trigone and internal sphincter whilst stimulation of beta-receptors in the bladder results in smooth muscle relaxation of the bladder wall and the net effect would be urinary continence.[6] Anticholinergic drive of olanzapine could be contributory as well.

We failed to locate any similar reports thus far of viloxazine use in ASD. Our report remains one of the earliest to report safe and effective use of viloxazine to tackle ADHD-like symptom profile in ASD, mitigating metabolic syndrome and nocturnal enuresis. This might open new treatment venues in such complicated clinical scenarios. That said, large rigorous studies are definitely needed to replicate these findings. ✤

Disclosures

Authors declare no competing interests nor financial affiliations.

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