HOPE® 1 demonstrates improvements in Clinical Global Impression (CGI) in patients with Autism Spectrum Disorder

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Background

As a sponsor of unregistered medicinal cannabis products in Australia, Zelira Therapeutics is responsible for approving the dispensing of each bottle to the patient.[1,2]

An essential part of improving the quality of care of patients is to understand how they are using the products, on the assumption that they are dosing to achieve clinical efficacy.

By understanding how patients are using Zelira products in the real-world setting, we are able to continue supporting clinicians and patients in their journey of achieving clinical improvement.

What is HOPE® 1?

HOPE® 1 was developed in the United States of America from a grassroots partnership with the Autism community. In October 2020, Zelira Therapeutics launched HOPE® 1 to Australian patients under the Therapeutic Goods Administration's (TGA) Special Access Scheme B and the Authorised Prescriber Scheme.

HOPE® 1 is a tincture blended with pharmaceutical grade refined, bleached and deodorised olive oil. It is a 1:1 THC:CBD ratio with 5mg/mL of THC, 5mg/mL of CBD. As a 1:1 THC:CBD product the TGA categorise HOPE® 1 as a Category 3 (balanced) product. In addition to THC and CBD, HOPE® 1 has Eucalyptol, Valencene and alpha-Pinene terpenes and a mild chocolate-mint flavouring.

HOPE® 1 is taken sublingually. The optimal dose of HOPE® 1 has not been established.

Dataset and analysis

The analysis in this paper is drawn from two independent sources namely the Zelira dispensing database and patient data captured by Emyria through their Emerald Clinics located in Western Australia (West Leederville), Victoria (Balwyn), and New South Wales (Sydney, Alstonville, Goonellabah) using a bespoke data platform that gathers ethically-sourced clinical evidence from their patients.

The Zelira dispensing database was commissioned by Zelira and is a cloud based electronic database that enables the request (by the pharmacist) and approval (by Zelira) of a dispense with the appropriate approval documentation (i.e. Special Access Scheme B approval letter, Authorised Prescriber Scheme approval letter).

The first 45 HOPE® 1 dispenses were analysed in this paper. As dispenses are continually occurring, patients were classified as active, lapsed or new. A lapsed patient was defined as not having received any product within the 4 month period prior to the data extraction date. New patients were defined as those having received at least a single bottle within the last 4 months of the data extraction date. All others were considered active.

More detailed data was captured on a subset of patients (n=19) that were dispensed HOPE® 1 and that attended an Emerald Clinic. Dosing information (time of day, amount), demographics, adverse events and concomitant medications were collected. Clinicians also completed the Clinical Global Impression (CGI)[3] questionnaire which consists of four questions:

1. Clinician rated *Severity of Illnes*s on a 0–7 scale;
2. Clinician rated *Global Improvement* on a 0–7 scale;
3. Therapeutic effect rated by the clinician as either Not assessed (0), Marked therapeutic effect (1), Moderate therapeutic effect (5), Minimal therapeutic effect (9), or Unchanged or Worse (13);
4. Side effects rated by the clinician best described as either None (0), Not significantly interfering with patient's functioning (1), Significantly interfering with patient's functioning (2), or Outweighs therapeutic effect (3).

From the CGI questions, the *CGI Efficacy Index* (total of the therapeutic effect [question 3] and the side effects [question 4]), the *CGI Improvement* (assigned to the response from question 2) and *CGI Severity* (assigned to the response from question 1) scores are calculated.

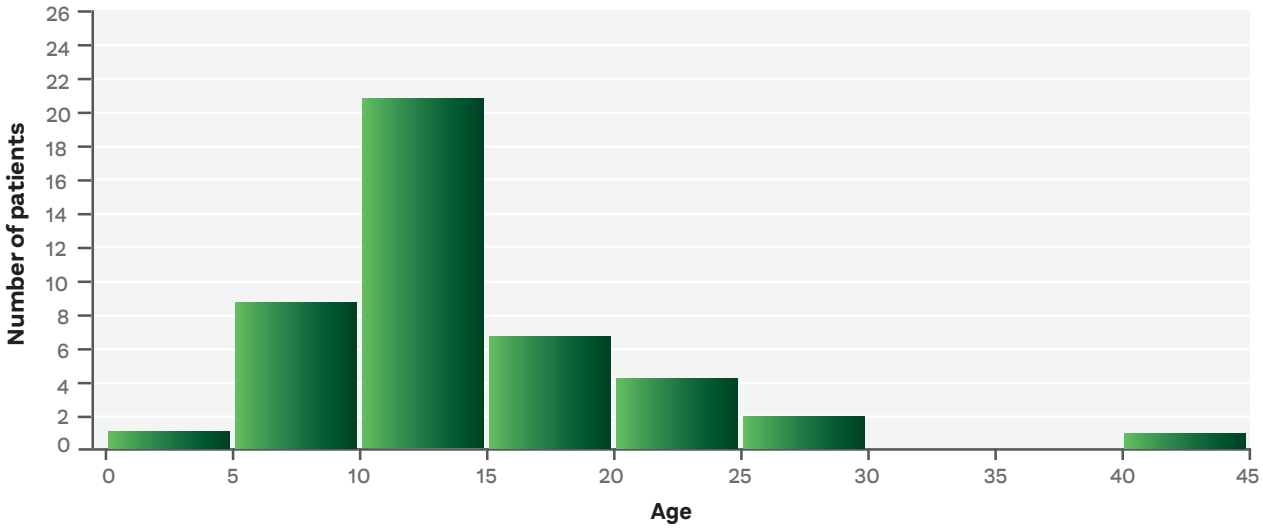
Results

Of the first 45 patients who were dispensed HOPE® 1, just over half were active patients (n=23, 51%), with new patients making up 35% (n=16) and lapsed patients making up 13% (n=6).

The primary indication for which HOPE® 1 was prescribed was for Autism Spectrum Disorders (ASD). Of those doctors who prescribed HOPE® 1, the majority (61%) were registered as General Practitioner, followed by Paediatrics and Child Health Specialists (35%) and then Psychiatrists (4%).

The mean age of active patients was 14.1 years of age with the youngest patient being 5.1 years of age **(Fig. 1)**. Those who did not continue taking HOPE® 1 were slightly younger with a mean age of 8.7 years.

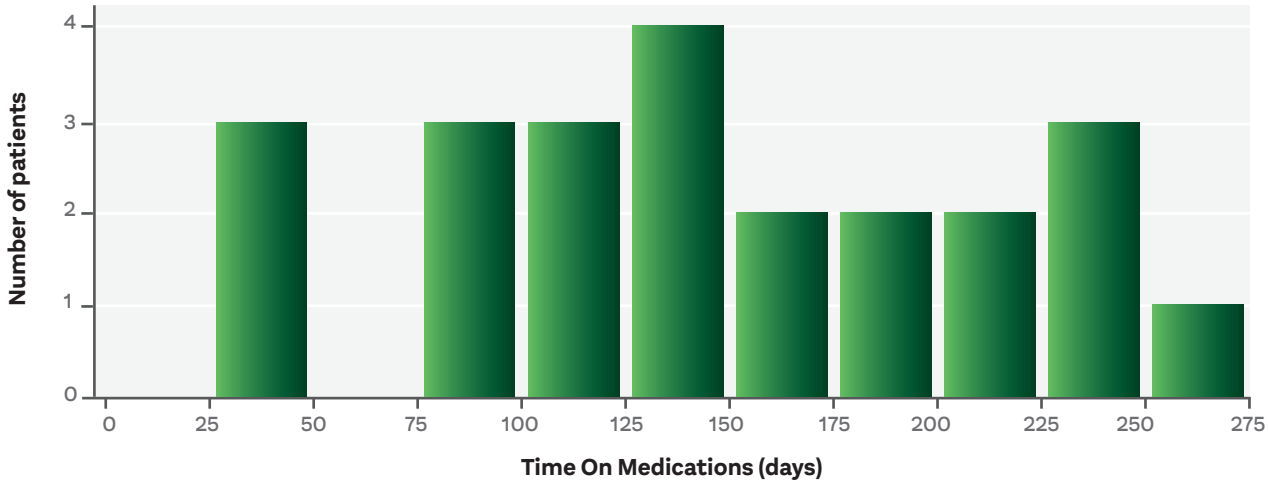
Figure 1: Age distribution of patients actively using HOPE® 1



Of the active patients, the maximum time to-date that a patient had taken HOPE® 1 was 8.9 months (or 270 days) **(Fig. 2)**. The mean time on treatment for active HOPE® 1 patients was 4.8 months with approximately 5.8 dispenses. Those who had lapsed had an average of 1.8 dispenses.

Of the first 45 patients who were dispensed HOPE® 1, nineteen (19) attended an Emerald Clinic; all were diagnosed with ASD and on average were assessed by a clinician as being 'Markedly ill' on the *CGI Severity index*. Twelve (12) patients at Emerald Clinics were 16 years of age or younger (range: 5 to 16 years of age) and seven (7) were over the age of 18 (range: 19 to 27 years of age).

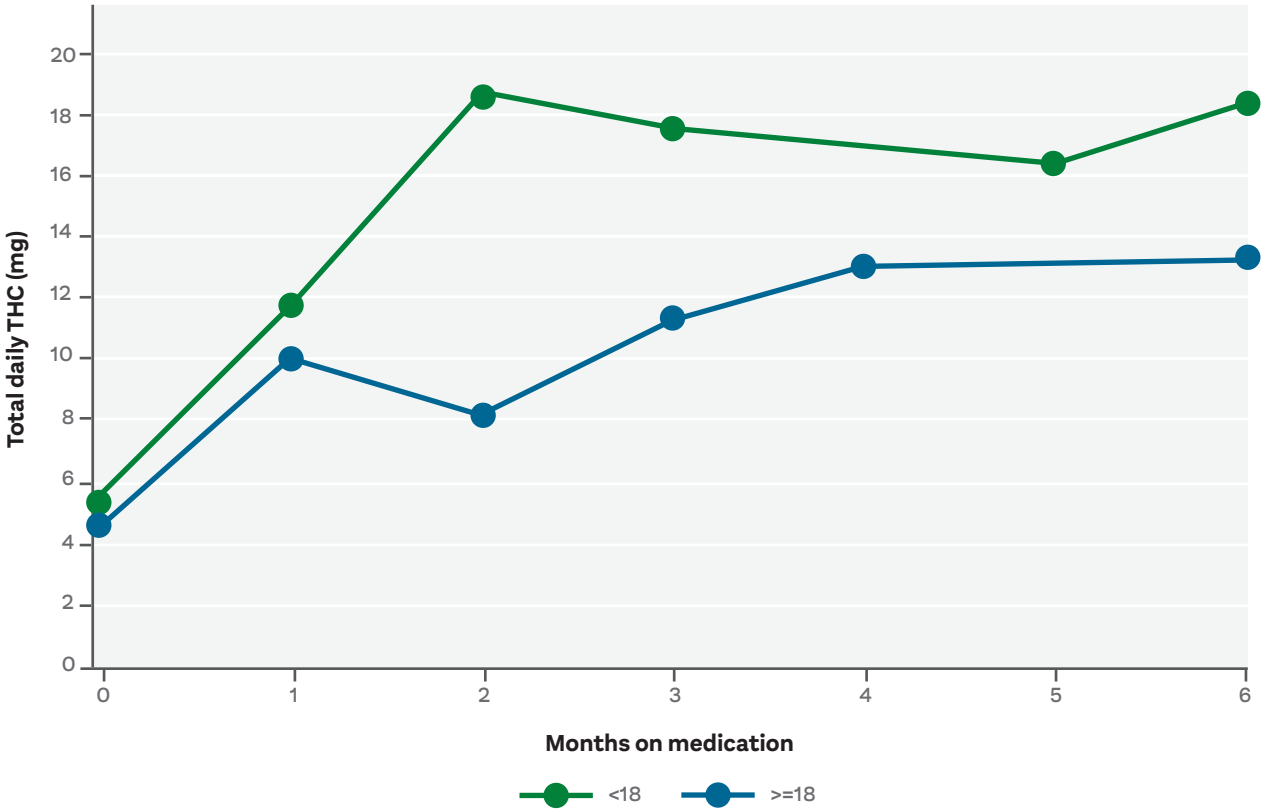
Figure 2: Distribution of the time HOPE® 1 active patients were on treatment



Emerald HOPE® 1 patients went through a dose escalation phase before reaching a maintenance phase. The dose escalation phase in general occurred over a 2–3 month period. Regardless of age (and by inference weight), Emerald Clinics patients started dosing with 1mL of HOPE® 1 per day (5mg THC: 5mg CBD) **(Fig. 3)**. The 1mL total daily dose was distributed across the day in approximately 0.25mL doses (1.25mg THC: 1.25mg CBD) given in the morning, afternoon, evening and at bedtime.

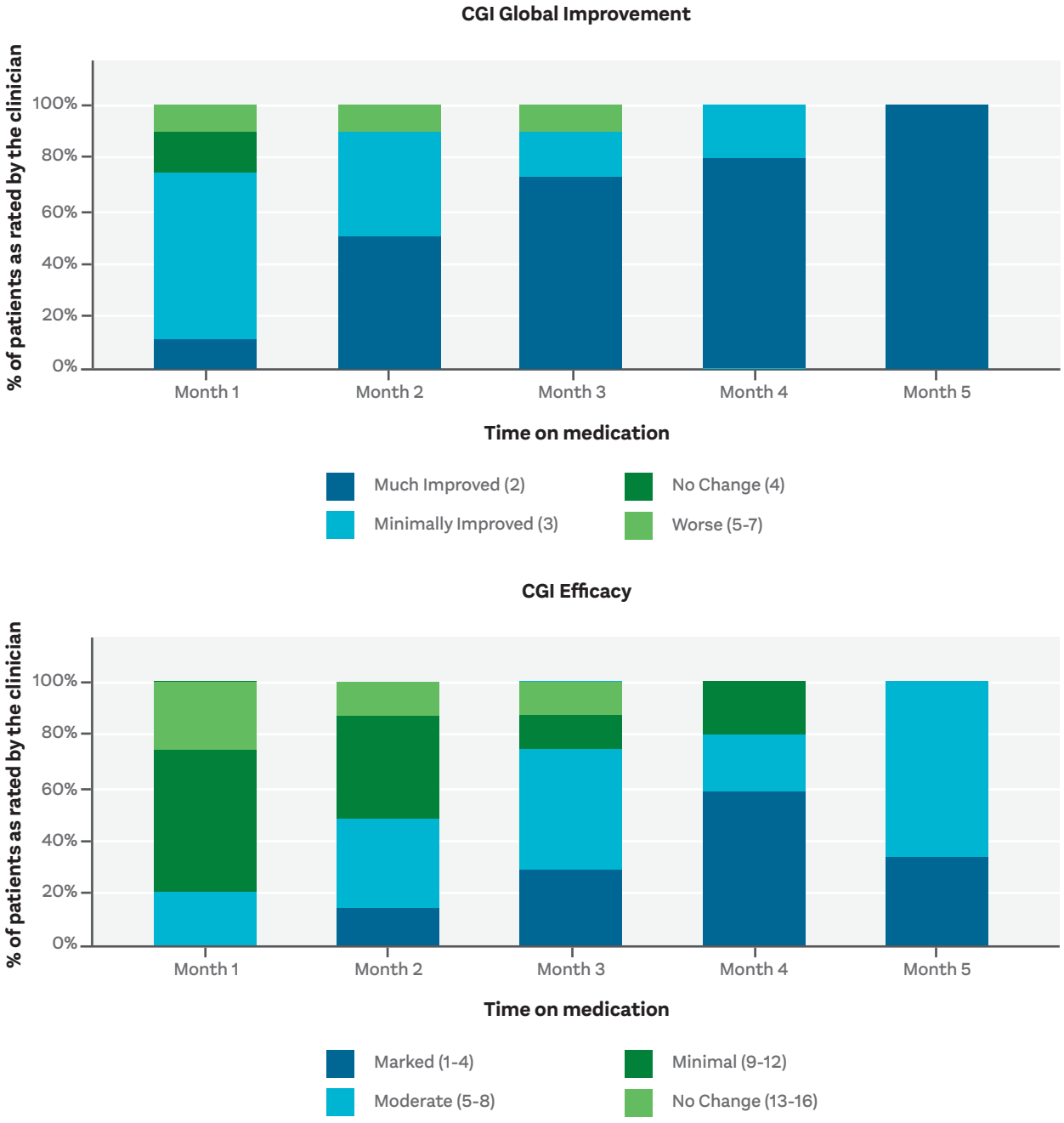
By the time Emerald HOPE® 1 patients reached their maintenance dose they were predominantly dosing twice a day (BID), morning and evening. The average maintenance dose for Emerald Clinics patients 16 years or younger was 2.5mL (12.6mg THC: 12.6mg CBD) of HOPE® 1 per day. Patients over the age of 18 years had a higher average maintenance dose of 3.6mL (17.9mg THC: 17.9mg CBD) of HOPE® 1 per day.

Figure 3: Average total daily THC dose of Emerald HOPE® 1 patients, by age group



Importantly, as the time patients spent on HOPE® 1 increased, so too on average did the clinicians rating of CGI Improvement; 67% of patients were rated as "Minimally improved" after 1 month on HOPE® 1 but after 2 months on HOPE® 1, 50% of patients were rated as "Much improved" and this increased to 75% of patients by 3 months, 80% of patients by 4 months and 100% of patients by 5 months **(Fig. 4)**.

Figure 4: Clinical Global Impression (CGI) Global Improvement and Efficacy scores of Emerald HOPE® 1 patients



After 1 month on HOPE® 1, clinicians rated 56% of patients as responding to HOPE® 1 treatment as 'Minimal' efficacy (score between 9–12) **(Fig. 4)**. After 3 months on HOPE® 1 clinicians rated the therapeutic effect of HOPE® 1 as 'Moderate' (scores between 5 – 8) in 50% of patients. A Moderate efficacy rating is described as 'Decided improvement, partial remission of symptoms' but with various levels of side effects. After 4 months on HOPE® 1 clinicians rated the therapeutic effect of HOPE® 1 as 'Marked' (scores between 1–4) in 60% of patients. A Marked therapeutic efficacy rating is described as 'Vast improvement. Complete or near complete remission of all symptoms' but with various levels of side effects. After 5 months on HOPE® 1, 67% of patients were rated as having achieved 'Moderate' efficacy.

A total of 25 adverse events occurred in 9 individuals. **The main adverse events were:**	• Sedation/sleepiness/lethargy/tiredness (occurred 9 times in 4 patients) • Change in appetite (5 times in 2 patients) • Neurological changes (hyperactivity/agitation/concentration difficulty/ emotional liability; 4 times in 4 patients) • Slurred speech (3 times in 1 patient) • Gastrointestinal (Constipation/Diarrhoea or loose stools; twice in 2 patients) • Eye redness (twice in 1 patient) • Mood (anxiety or panic attack; once in 1 patient)
Of the Emerald Clinics HOPE® 1 patients, 7 reported being on at least one concomitant medication while on HOPE® 1. Patients reported being on:	• Benzodiazepines (Clonazepam, Lorazepam) • Selective Serotonin Reuptake Inhibitors (Fluvoxamine, Citalopram) • Anti-psychotics (Brexpipraxole, Risperidone) • Alpha-agonist hypotensive agents (Clonidine) • Beta Blockers (Propranolol) • Anti-epileptics (Valproate sodium) • Stimulants / Non-stimulants (Lisdexamfetamine, Intuniv) • Hormones (Melatonin, Agomelatine)

Conclusions

HOPE® 1 is a 1:1 THC:CBD ratio product containing 5mg/mL of THC and 5mg/mL of CBD and is categorised by the TGA as a Category 3 (balanced) product.

In the Australian real-world setting, HOPE® 1 was typically prescribed for ASD patients from as young as 5 years of age. Minimal adverse events were reported in a limited number of patients on HOPE® 1 over an extended period of time. Patients also maintained their normal concomitant medications. Thus HOPE® 1 appears to be safe in this population.

Anecdotally, clinicians have preferred to prescribe CBD-enriched medicinal cannabis products (i.e. 1:20 THC:CBD ratio products) for the treatment of paediatric patients with ASD. Indeed, the majority of research on the safety and efficacy of medicinal cannabis to treat ASD behaviours has assessed 1:20 THC:CBD ratio products.[4-6] In these studies, the typical effective daily dose ranged from 4-20mg THC with 45-256mg CBD. However, a recent study in a mouse model of ASD demonstrated that "CBD enrichment of medical cannabis is not necessary for treating the autistic-like phenotypes of InsG3680 Shank 3 mutant mice. Furthermore, our results suggest that THC-based medical cannabis oil is preferable for that purpose".[7] The study also found that the long-term use of THC did not significantly harm the working memory and motivation of the ASD mice compared to control mice.

In support of the above emerging research and highlighting the importance of THC in modulating behavioural and repetitive ASD behaviours, HOPE® 1 paediatric patients appeared to have an effective maintenance dose of 12.6mg THC: 12.6mg CBD (2.5mL of HOPE® 1). This daily dose is in the middle of the THC concentration ranges that paediatric patients on 1:20 THC:CBD products consume. Further, the daily dose of total cannabinoids (25.2 mg) and volume (2.5mL) that HOPE® 1 paediatric patients consume is significantly less than is necessary for CBD dominant products. Thus HOPE® 1 patients are able to achieve clinical improvement whilst consuming less total cannabinoids.

Dosing Schedule Recommendations

Traditionally it is recommended that for medicinal cannabis products the starting doses should be low and increased over time to monitor the potential negative effects. Without close supervision, patients take several months to up-titrate (escalate dose). However, in a more structured approach, dose escalation can be done over a 2 to 4 week period where patients spend at least 2 to 3 days at each dose level before increasing to the next level until an unacceptable tolerability occurs. Following the dose escalation period, patients enter what is known as the maintenance phase, where they achieve maximal benefits with minimal side effects (or dose maintenance phase). It is recommended that HOPE® 1 is taken BID with afternoon and bedtime doses added if required.

Based on the graduated dropper provided with HOPE® 1 and the subset analysis of the amount and dosing pattern in which patients take HOPE® 1 a suggested dosing schedule is provided below.

Patients under 16 years of age:

Phase	Morning	Afternoon	Evening	Bedtime	Total volume	Total THC
Dosing pattern	**Main dose**	**Optional**	**Secondary dose**	**Optional**		
Escalation	0.25mL	0.25mL	0.25mL	0.25mL	1.00mL	5.00mg
	0.50mL	0.25mL	0.50mL	0.25mL	1.50mL	7.50mg
	0.75mL	0.25mL	0.75mL	0.25mL	2.00mL	10.00mg
Maintenance	0.75mL	0.50mL	0.75mL	0.50mL	2.50mL	12.5mg

Patients over 18 years of age:

Phase	Morning	Afternoon	Evening	Bedtime	Total volume	Total THC
Dosing pattern	**Main dose**	**Optional**	**Secondary dose**	**Optional**		
Escalation	0.25mL	0.25mL	0.25mL	0.25mL	1.00mL	5.00mg
	0.50mL	0.25mL	0.50mL	0.25mL	1.50mL	7.50mg
	0.75mL	0.25mL	0.75mL	0.25mL	2.00mL	10.00mg
	0.75mL	0.50mL	0.75mL	0.50mL	2.50mL	12.5mg
Maintenance	1.00mL	0.50mL	1.00mL	0.50mL	3.00mL	15.0mg
	1.50mL	1.00mL	1.00mL	0.50mL	4.00mL	20.0mg

Patient feedback

HOPE® 1 Patient Case Study

- Young male patient of primary school age with a diagnosis of autism spectrum disorder (ASD)
- Prior to HOPE® 1, troublesome behaviours included: anger and aggression, inability to attend school, verbal abuse, self-injurious behaviour, violent coercion (physically and verbally), physical destruction of property, intimidation of younger siblings, self-loathing
- Prior treatment with extensive therapies, without significant benefit, including fluoxetine, paroxetine, mirtazapine, fluvoxamine, sertraline, citalopram, risperidone, aripiprazole, quetiapine and CBD oil
- Adverse reactions to treatments including weight gain, restless leg syndrome and mental obfuscation (leading to disengagement from school).
- Continued to have periods of anger and aggression (both verbal and physical) that worsened as he got older.

February 2021, HOPE® 1 initiated. After two weeks titration there was a remarkable decrease in the frequency and intensity of aggressive behaviours and persistent irritability. His repertoire of emotional language broadened, and he was showing early-stage impulse control (walking away when upset in an attempt to self-regulate).

Up to this point, the family have started discussions with the school about reintegration back into education and the classroom which didn't seem like it would be an option.

The family believed the teen would be in and out of psychiatric care and the justice system based on his history.

Medical notes from treating physician:

Marked improvement in behaviour (80%) with less aggression and agitation and a greater ability for impulse control, to divert and reflect on his behaviours. His "meltdowns" are fewer, shorter and less intense. He has engaged with school and is learning and listening more. He is eating more diverse foods and more willing to try different flavours and textures.

Quote from mother.

"What HOPE® has offered us is exactly what the name states: Hope for a future for our son."

References

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