Qelbree (viloxazine) for Attention Deficit Hyperactivity Disorder (ADHD)

Prepared by Jeeseon Rosa Kim, PharmD.

Presented by Shoshana Steinmetz, PharmD.

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Attention Deficit Hyperactivity Disorder (ADHD)

- Prevalence
  - Children: ~ 6.1 million (9.4%) in 2016
  - Adults: ~4.4%
- Comorbid psychiatric disorders are common in both adults and children
  - Anxiety, behavior/conduct problems, mood disorders, substance abuse, etc.

Attention-deficit/hyperactivity disorder (ADHD). Center for Disease Control and Prevention. 2020.
Bukstein O. UpToDate. Updated March 26, 2021. Accessed September 10, 2021

Attention Deficit Hyperactivity Disorder (ADHD)

- Diagnosis based on DSM-5 criteria
- Evaluation
  - ADHD rating scales (ADHD-RS)
  - Conners Rating Scale
- Treatment
  - Pre-school: behavioral therapy
  - Children and adolescents (6-17): pharmacological treatments
  - Adults: pharmacological treatments

Post RE, et al. Am Fam Physician. 2012;85(9):890-6.
Wolraich ML et al. Pediatrics. 2019;144(4):e20192528.

Attention Deficit Hyperactivity Disorder (ADHD)

Stimulants

- May use in children (≥ 6 y/o), adolescents, and adults
- Strong and sufficient evidence for management of ADHD

Non-stimulants

- May use in children, adolescents, and adults
  - FDA approval for children and adolescents (6-17 y/o) except for atomoxetine
- Not as strong evidence compared to stimulants
  - Atomoxetine is recommended as a first line agent along with other stimulants in adults

Post RE, et al. Am Fam Physician. 2012;85(9):890-6.
Wolraich ML et al. Pediatrics. 2019;144(4):e20192528.
ADHD medication guide. Cohen Children's Medical Center. Updated September 1, 2021. Accessed September 10, 2021

Qelbree (Viloxazine)

- Approved April 2, 2021
- Indication: treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients (6-17 y/o)
- MOA: selective norepinephrine reuptake inhibitor (non-stimulant)

Qelbree. Package insert. Supernus Pharmaceuticals Inc; 2021

Qelbree (Viloxazine)

- Dosage form: oral capsule
- Dose:
  - 6-11 y/o: 100 mg once daily. Titrate 100 mg weekly. Max dose 400 mg/day
  - 12-17 y/o: 200 mg once daily. Titrate 200 mg weekly. Max dose 400 mg/day
  - Renal impairment: 100 mg/day. Titrate 50 – 100 mg weekly. Max dose 200 mg/day
- May open and sprinkled onto applesauce

Qelbree. Package insert. Supernus Pharmaceuticals Inc; 2021

Qelbree (Viloxazine)

- Drug interactions:
  - MAOI (Selegiline, rasagiline, phenelzine, etc.)
    - Hypertensive crisis
    - Do not use together or within 2 weeks of MAOI d/c
  - Sensitive to CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range (alosetron, duloxetine, ramelteon, tasimelteon, tizanidine, theophylline)
    - Increased exposure (but not peak exposure) of the CYP1A2 substrates (↑ toxicity)
    - Do not use together
  - Moderate sensitive CYP1A2 substrates (clozapine, pirfenidone)
    - Increased exposure (but not peak exposure) of the CYP1A2 substrates (↑ toxicity)
    - Concurrent use not recommended; may warrant dose reduction

Qelbree. Package insert. Supernus Pharmaceuticals Inc; 2021

Qelbree (Viloxazine)

- Drug interactions:
  - CYP2D6 substrates (atomoxetine, desipramine, dextromethorphan, nortriptyline, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine, and risperidone)
    - Increased exposure of the CYP2D6 substrates (↑ toxicity)
    - Monitor and adjust dosage of CYP2D6 substrates, as clinically indicated
  - CYP3A4 substrates (darunavir, saquinavir, simvastatin, tipranavir, alfentanil, avanafil, etc.)
    - Increased exposure of the CYP3A4 substrates (↑ toxicity)
    - Monitor and adjust dosage of CYP3A4 substrates, as clinically indicated

Qelbree. Package insert. Supernus Pharmaceuticals Inc; 2021

Qelbree (Viloxazine)

- Contraindications
  - Concurrent or h/o MAOI use within 14 days
  - Concomitant use of sensitive CYP1A2 substrates or CYP1A2 substrates with narrow therapeutic range
- Boxed warning:
  - Suicidal thoughts and behaviors
- Adverse reactions (≥ 5%)
  - Somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability

Qelbree. Package insert. Supernus Pharmaceuticals Inc; 2021

Clinical Evidence

Study design	Randomized, placebo-controlled, phase III trial
Intervention	Viloxazine 100 mg/day, 200 mg/day, placebo • Subjects were required to stop taking any other ADHD medications starting at least 1 week prior to randomization and throughout the study
Study population	School-age children (6-11 y/o) with ADHD
Inclusion criteria	Diagnosis of ADHD, ADHD-RS-5 total score ≥ 28, CGI-S ≥4
Exclusion criteria	Concurrent psychiatric/neurological disorders (except oppositional defiant disorder or MDD that is currently and has been free of symptoms for the past 6 months), systemic disease, evidence of suicidality within 6 months of screening
Endpoints	Primary: change from baseline (CFB) in the ADHD-RS-5 total score at end of study (EOS; week 6) Key secondary endpoints: CGI score at EOS, CFB in the Conners 3-PS Composite T-score at EOS, CFB in the WFIRS-P total average score at EOS

Nasser A, et al. Clin Ther. 2020;42(8):1452-1466.

Clinical Evidence – Results

Table I. Demographic and baseline characteristics in the intent-to-treat (ITT) population.

Characteristic	Placebo	SPN-812		Overall
		100 mg/day	200 mg/day	
N (ITT)	155	147	158	460
Age, mean (SD), y	8.5 (1.7)	8.5 (1.7)	8.5 (1.7)	8.5 (1.7)
Sex, n (%)				
Male	97 (62.6)	94 (63.9)	99 (62.7)	290 (63.0)
Female	58 (37.4)	53 (36.1)	59 (37.3)	170 (37.0)
Ethnicity, n (%)				
Hispanic or Latino	32 (20.6)	38 (25.9)	51 (32.3)	121 (26.3)
Not Hispanic or Latino	123 (79.4)	108 (73.5)	107 (67.7)	338 (73.5)
Race, n (%)				
American-Indian or Alaska Native	1 (0.6)	1 (0.7)	0	2 (0.4)
Asian	1 (0.6)	0	0	1 (0.2)
Black or African American	69 (44.5)	63 (42.9)	69 (43.7)	201 (43.7)
Multiple	7 (4.5)	7 (4.8)	6 (3.8)	20 (4.3)
White	77 (49.7)	76 (51.7)	83 (52.5)	236 (51.3)
Weight, mean (SD), kg	31.1 (8.0)	31.7 (8.9)	31.8 (8.4)	31.5 (8.4)
Body mass index, mean (SD), kg/m^2	16.9 (2.2)	17.3 (2.2)	17.2 (2.4)	17.1 (2.3)
ADHD-RS-5, mean (SD)				
Total score	43.6 (7.1)	45.0 (6.5)	44.0 (6.8)	44.2 (6.8)
Inattention	22.5 (3.8)	22.8 (3.2)	22.9 (3.5)	22.7 (3.5)
Hyperactivity/Impulsivity	21.1 (4.9)	22.2 (4.7)	21.1 (5.2)	21.5 (4.9)
CGI-S score, mean (SD)	4.8 (0.7)	4.8 (0.8)	4.8 (0.7)	ND

ADHD-RS-5 = ADHD Rating Scale-5; CGI-S = Clinical Global Impression–Severity of Illness; ND = not determined; SD = standard deviation.

- Young, male, non-Hispanic, white or black
- Frequent ADHD symptoms
  - Similar frequency between inattention and hyperactivity/impulsivity symptoms
- Moderate illness

Nasser A, et al. Clin Ther. 2020;42(8):1452-1466.

Clinical Evidence – Results

- Viloxazine significantly improved ADHD-RS-5 scores by the end of study (EOS)
  - Significance is seen starting week 1 and maintained till EOS

Table II. ADHD Rating Scale-5 (ADHD-RS-5) results in the intent-to-treat population at end of study by treatment group.

ADHD-RS-5 Measure	Placebo (n = 155)	SPN-812	
		100 mg/day (n = 147)	200 mg/day (n = 158)
CFB, LS mean (SE)			
Total score	−10.9 (1.14)	−16.6 (1.16)*	−17.7 (1.12)†
Inattention subscale‡	−5.7 (0.60)	−8.6 (0.62)*	−9.2 (0.60)†
Hyperactivity/Impulsivity subscale‡	−5.5 (0.59)	−8.0 (0.60)*	−8.7 (0.58)†
50% responder rate§	31 (19.8%)	50 (34.2%)*	65 (41.2%)†

* $P < 0.05$ versus placebo.
† $P < 0.0001$ versus placebo.
‡ P values derived from ANCOVA model.
§ P values derived from logistic regression.

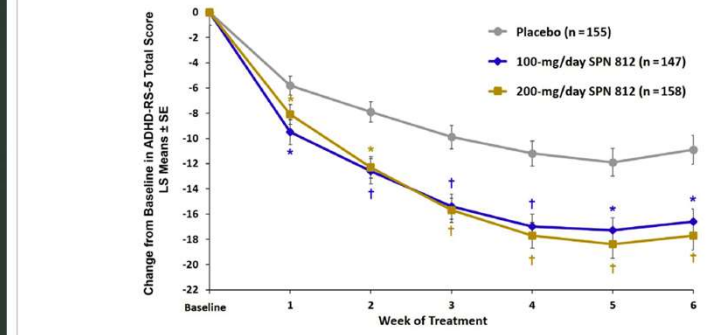

Figure 2. Analysis of change from baseline in ADHD-Rating Scale-5 (ADHD-RS-5) Total score in the intent-to-treat population. LS = least squares; SE = standard error. *$P < 0.05$. †$P < 0.0001$.

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Clinical Evidence – Results

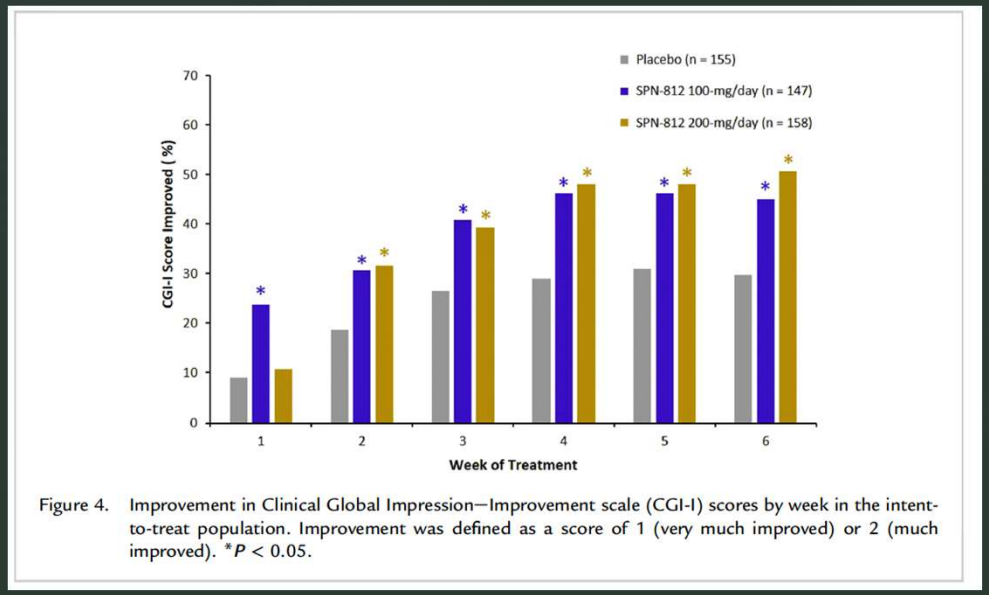

Figure 4. Improvement in Clinical Global Impression—Improvement scale (CGI-I) scores by week in the intent-to-treat population. Improvement was defined as a score of 1 (very much improved) or 2 (much improved). *$P < 0.05$.

- Significantly more patients in viloxazine group were in CGI-I 1 or 2 (very much improved or much improved)

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Clinical Evidence – Results

Table III. Conners 3—Parent Short Form (Conners 3—PS) and Weiss Functional Impairment Rating Scale—Parent Form (WFIRS—P) results by treatment group. Values indicate change from baseline and are given as least squares mean (SE); P values are derived from an ANCOVA model.

Measure	Placebo (n = 155)	SPN-812	
		100 mg	200 mg
		(n = 147)	(n = 158)
Conners 3—PS (T-score)			
Composite	−4.8 (0.81)	−9.1 (0.83)*	−9.2 (0.82)*
Content Scales			
Inattention	−6.6 (1.06)	−11.1 (1.09)*	−11.1 (1.06)*
Hyperactivity	−6.0 (1.06)	−10.0 (1.08)*	−10.8 (1.06)*
Learning problems	−3.2 (0.91)	−6.4 (0.94)*	−6.3 (0.91)*
Executive functioning	−6.5 (0.99)	−11.9 (1.03)*	−10.8 (0.99)*
Defiance/aggression	−4.3 (1.12)	−6.0 (1.13)	−7.9 (1.11)*
Peer relations	−2.7 (1.19)	−8.8 (1.21)*	−7.8 (1.18)*
WFIRS—P (average score)			
Total	−0.22 (0.033)	−0.36 (0.033)*	−0.39 (0.032)*
Domains			
Family	−0.26 (0.048)	−0.41 (0.048)*	−0.51 (0.047)*
Self-concept	−0.21 (0.044)	−0.25 (0.045)	−0.27 (0.043)
School	−0.28 (0.051)	−0.51 (0.052)*	−0.52 (0.051)*
Life skills	−0.27 (0.038)	−0.36 (0.038)	−0.34 (0.037)
Social activities	−0.20 (0.043)	−0.34 (0.044)*	−0.37 (0.043)*
Risky activities	−0.12 (0.028)	−0.21 (0.028)*	−0.24 (0.028)*

*$P < 0.05$ versus placebo. SE = standard error.

- Viloxazine significantly improved Conners 3-PS and WFIRS-P scores

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Clinical Evidence – Results

Table IV. Summary of adverse events (AEs) using the safety population. Values are given as n (%).

Safety Measure (Preferred Term)	Placebo (n = 159)	SPN-812		
		100 mg/day (n = 154)	200 mg/day (n = 161)	Overall (n = 315)
At least 1 AE	47 (29.6)	74 (48.1)	77 (47.8)	151 (47.9)
Treatment-related AEs ≥5%				
Somnolence	3 (1.9)	14 (9.1)	14 (8.7)	28 (8.9)
Decreased appetite	0	7 (4.5)	12 (7.5)	19 (6.0)
Headache	3 (1.9)	7 (4.5)	10 (6.2)	17 (5.4)
AEs leading to discontinuation				
Total	2 (1.3)	5 (3.2)	2 (1.2)	7 (2.2)
Tachycardia	0	1 (0.6)	0	1 (0.3)
Fatigue	0	1 (0.6)	0	1 (0.3)
ECG T-wave inversion	0	1 (0.6)	0	1 (0.3)
Decreased appetite	0	0	1 (0.6)	1 (0.3)
Dizziness	0	1 (0.6)	0	1 (0.3)
Aggression	1 (0.6)	1 (0.6)	0	1 (0.3)
Agitation	1 (0.6)	0	0	0
Conduct disorder	0	1 (0.6)	0	1 (0.3)
Pyromania	0	1 (0.6)	0	1 (0.3)
Sleep terror	0	0	1 (0.6)	1 (0.3)

- Higher incidence of AE reported with viloxazine
  - Similar between the two doses
- Most common: somnolence, decreased appetite, and headache
- AEs leading to treatment discontinuations:
  - mostly CV or CNs related
  - Infrequently reported

Nasser A, et al. Clin Ther. 2020;42(8):1452-1466.

Clinical Evidence – Discussion and Conclusion

- Findings suggest viloxazine is an effective and the improvements are clinically meaningful
- Unclear what other treatments the study patients received previously
- No comparative efficacy
- Only studied and approved for use in children
  - At AmidaCare, majority of ADHD patients are adults (currently)
- Excluded patients with other psychiatric disorders
- Potential drug interactions with CYP2D6, CYP3A4 substrates/inhibitors
- Viloxazine can be a nonstimulant option for ADHD treatments; however, use at AmidaCare may be limited to small group

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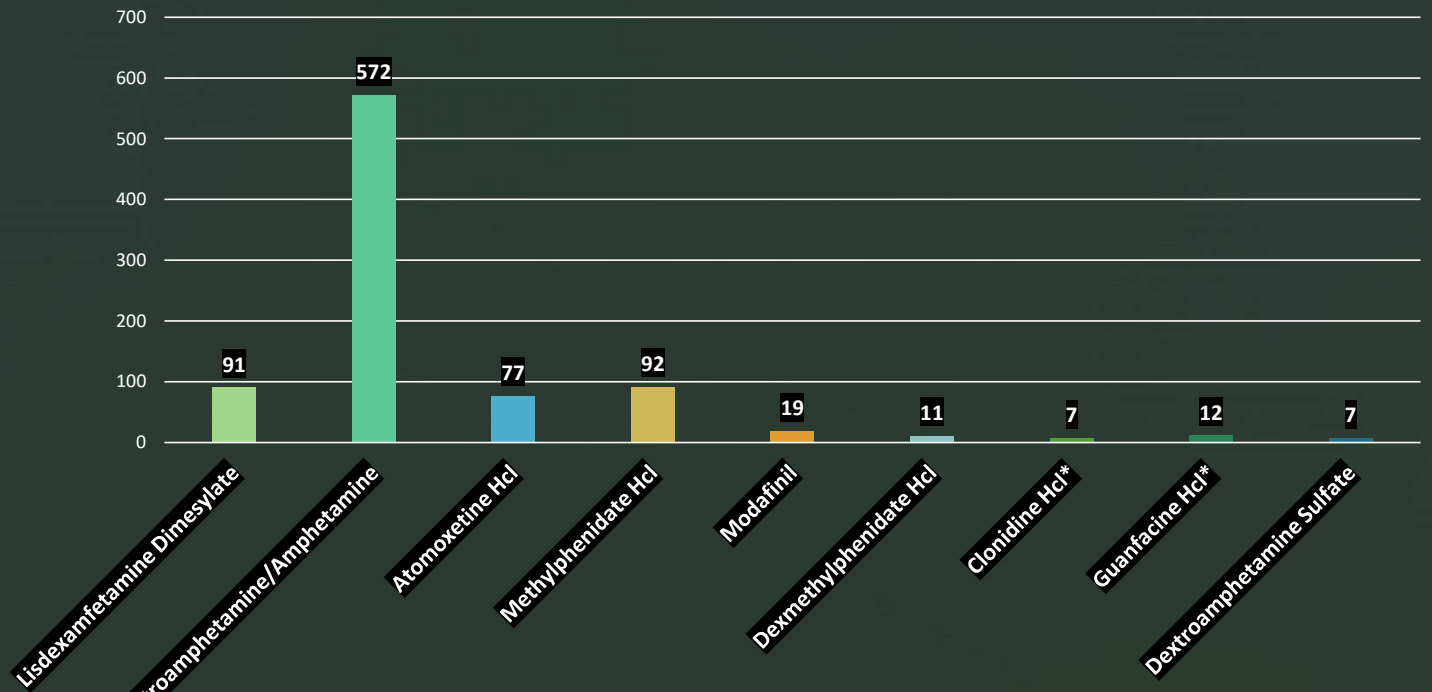
AmidaCare Utilization



Medication Cost Analysis

Drug	30-day supplies (at max dose)
Qelbree	$358.80
Lisdexamphetamine (Vyvanse)	$401.979
Dextroamphetamine/ amphetamine (Adderall)	IR $538.80
	ER $512.58
Atomoxetine	$500.58
Guanfacine ER (Intuniv)	$349.5
Clonidine (Kapvay)	$1,164
Modafinil	$1,979.98

Drug	30-day supplies (at max dose)
Dextroamphetamine	$449.92
Dexmethylphenidate	IR $84
	ER $255.26
Methylphenidate	Tab: $131.07 TER: $617.31 LACap: $444.46

IBM Micromedex Redbook. Accessed September 10, 2021.

Formulary Recommendation

- Non-formulary, prior authorization
  - PA criteria
    - Age 6-17
    - Diagnosis of ADHD
    - Unable to take stimulants
    - No concurrent psychiatric disorders except for:
      - Oppositional defiant disorder
      - MDD that is currently and has been free of symptoms for the past 6 months
    - Not currently on regimens that are contraindicated
    - No evidence of suicidal behaviors/ideation in the past 6 months

References

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