A Tale of 2 Profiles: Hemodynamic Influence of Atomoxetine Under Intensive Observation Versus Clinical Trial Observation

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Introduction

- Atomoxetine is a selective norepinephrine reuptake inhibitor approved for attention-deficit hyperactivity disorder (ADHD) treatment
  - The maximum approved dose in the United States is 1.4 mg/kg or 100 mg, whichever is less, irrespective of CYP2D6 metabolizing status
- The metabolism of atomoxetine is highly dependent on CYP2D6
  - $C_{max,ss}$: Poor metabolizer (PM) 5x greater than extensive metabolizer (EM)
  - AUC: PM 10x greater than EM
  - A 20 mg BID dose in PMs approximates the exposure of a 60 mg BID dose in EMs
- A TQT study was conducted in PMs at doses of 20 mg BID to approximate exposure at maximum dose in EMs and 60 mg BID to result in maximum exposure at maximum approved dose
  - Systematic hemodynamic assessment (supine pulse and blood pressure and standing pulse and blood pressure at 2 minutes) following each ECG replicate set acquisition at baseline (2 days) and Day 7 of treatment
  - Continuous 12-lead ECG recording at baseline, Day 1 and Day 7 of treatment

Comparison of Mean Changes from Baseline in Systolic Blood Pressure and Orthostatic Drop Between Atomoxetine and Placebo

- Both doses of atomoxetine increased supine systolic BP relative to placebo.
- Atomoxetine was associated with a significant orthostatic drop in BP.

Time Postdose (hr)	ATX 20-mg BID - Placebo Mean (2-sided 95% CI) mmHg		ATX 60-mg BID - Placebo Mean (2-sided 95% CI) mmHg	
	Supine*	Orthostatic Drop*	Supine*	Orthostatic Drop*
1	6.4 (4.1, 8.8)	4.5 (1.1, 7.7)	8.2 (5.8, 10.5)	6.6 (3.3, 9.9)
2	***9.0 (6.7, 11.4)***	7.1 (3.9, 10.4)	***10.3 (7.9, 12.6)***	7.3 (3.9, 10.6)
4	6.1 (3.7, 8.4)	7.3 (4.0, 10.6)	9.0 (6.6, 11.3)	7.9 (4.6, 11.3)
6	8.6 (6.3, 11.0)	***9.4 (6.2, 12.8)***	9.1 (6.7, 11.5)	8.1 (4.8, 11.5)
12	4.0 (1.6, 6.3)	6.7 (3.4, 10.0)	7.9 (5.6, 10.3)	***9.4 (6.1, 12.7)***

* Baseline = measurement on Day -1; ATX = atomoxetine; BP = blood pressure.

Comparison of Mean Changes from Baseline in Diastolic Blood Pressure and Orthostatic Drop Between Atomoxetine and Placebo

- Both doses of atomoxetine increased supine diastolic BP relative to placebo.
- Atomoxetine was associated with a significant orthostatic drop in BP.

Time Postdose (hr)	ATX 20-mg BID - Placebo Mean (2-sided 95% CI) mmHg		ATX 60-mg BID - Placebo Mean (2-sided 95% CI) mmHg	
	Supine*	Orthostatic Drop*	Supine*	Orthostatic Drop*
1	5.7 (3.8, 7.6)	2.3 (-0.2, 4.9)	9.0 (7.2, 10.9)	5.7 (3.3, 8.1)
2	5.7 (3.8, 7.6)	0.9 (-1.6, 3.4)	9.0 (7.1, 10.8)	4.5 (2.0, 6.9)
4	***6.3 (4.4, 8.3)***	3.6 (1.1, 6.2)	***9.6 (7.7, 11.4)***	4.7 (2.3, 7.2)
6	6.0 (4.1, 7.9)	***4.6 (2.1, 7.2)***	8.8 (7.0, 10.6)	***5.9 (3.5, 8.4)***
12	5.8 (3.9, 7.7)	1.9 (-0.6, 4.4)	8.8 (7.0, 10.6)	4.3 (1.9, 6.8)

* Baseline = measurement on Day -1; ATX = atomoxetine; BP = blood pressure.

Comparison of Mean Changes from Baseline in Heart Rate (Obtained by Machine-Measured Peripheral Pulse) and Orthostatic Rise Between Atomoxetine and Placebo

- Both doses of atomoxetine increased HR relative to placebo, with a positive dose-response.
- Atomoxetine was associated with a significant orthostatic rise in HR relative to placebo.

Time Postdose (hr)	ATX 20-mg BID - Placebo Mean (2-sided 95% CI) bpm		ATX 60-mg BID - Placebo Mean (2-sided 95% CI) bpm	
	Supine*	Orthostatic Rise*	Supine*	Orthostatic Rise*
1	***9.9 (8.0, 11.8)***	10.2 (7.0, 13.2)	12.1 (10.1, 14.1)	11.4 (8.5, 14.6)
2	8.8 (7.0, 10.7)	13.9 (10.8, 17.0)	***14.0 (12.0, 16.0)***	12.2 (9.1, 15.2)
4	9.7 (7.9, 11.6)	***14.7 (11.6, 17.7)***	13.4 (11.4, 15.4)	12.3 (9.3, 15.3)
6	7.8 (5.9, 9.6)	12.3 (9.1, 15.3)	11.6 (9.6, 13.6)	12.4 (9.3, 15.4)
12	9.1 (7.3, 11.0)	11.6 (8.6, 14.7)	11.3 (9.3, 13.3)	***15.2 (12.2, 18.3)***

* Baseline = measurement on Day -1 ; ATX = atomoxetine; bpm = beats per minute; HR = heart rate.

Comparison of Mean Changes from Baseline in Heart Rate (Obtained by 10-second ECG) Between Atomoxetine and Placebo

- Both doses of atomoxetine increased HR relative to placebo.
- HR increase greater with 60 mg BID than 20 mg BID.

Time Postdose (hr)	ATX 20-mg BID - Placebo Mean (2-sided 95% CI) bpm	ATX 60-mg BID - Placebo Mean (2-sided 95% CI) bpm
1	10.5 (8.9, 12.0)	12.7 (11.1, 14.2)
2	10.5 (9.0, 12.1)	13.7 (12.2, 15.3)
4	***11.2 (9.7, 12.8)***	***15.1 (13.5, 16.6)***
6	9.5 (7.9, 11.0)	13.1 (11.5, 14.6)
12	9.4 (7.9, 11.0)	11.6 (10.0, 13.2)

Baseline = mean of measures on Days -2 and -1; ATX = atomoxetine; bpm = beats per minute; ECG = electrocardiogram; HR = heart rate.

Comparison of Mean Changes from Baseline in Heart Rate (Obtained by 24-hour Continuous ECG Monitoring) Between Atomoxetine and Placebo for 4-Hour Intervals

- 24-hour continuous ECG monitoring data were consistent with 10-second ECG and peripheral pulse results

		ATX 20-mg BID		ATX 60-mg BID	
Time Interval	**Day**	**Difference from Placebo (95% CI) bpm**	**n**	**Difference from Placebo (95% CI) bpm**	**n**
8 am-noon	1	0.1 (-1.4, 1.5)	80	0.4 (-1.03, 1.84)	84
	7	10.2 (8.7, 11.7)	76	13.6 (12.1, 15.1)	78
Noon-4 pm	1	3.3 (1.7, 5.0)	80	2.6 (0.9, 4.2)	84
	7	***11.1*** (9.4, 12.8)	76	***13.6*** (11.9, 15.3)	78
4 pm-8 pm	1	2.2 (0.5, 4.0)	80	2.6 (0.8, 4.3)	84
	7	9.5 (7.6, 11.3)	76	12.3 (10.5, 14.1)	78
8 pm-midnight	1	1.6 (0.1, 3.2)	80	1.7 (0.2, 3.2)	84
	7	8.7 (7.1, 10.3)	76	12.0 (10.4, 13.6)	78
Midnight-4 am	1	4.9 (3.6, 6.1)	80	5.8 (4.6, 7.0)	84
	7	9.2 (7.9, 10.5)	76	13.5 (12.2, 14.8)	77
4 am-8 am	1	6.8 (5.6, 8.1)	80	7.5 (6.2, 8.7)	84
	7	9.7 (8.4, 11.0)	76	12.8 (11.5, 14.1)	77

Baseline = mean of measures on Day -2 or Day -1. If both Day -2 and Day -1 data were available, the data were averaged to provide a single baseline value .

Comparison of Maximum Mean Changes from Baseline in Hemodynamic Parameters Between Test Drugs and Placebo

	ATX 60 mg BID - Placebo		Methylphenidate 60 mg/day - Placebo	
	Day 1	Day 5	Day 1	Day 5
Heart rate (bpm)	9.75	5.61	18.44	24.76
Systolic BP (mmHg)	13.85	-2.40	16.18	13.77
Diastolic BP (mmHg)	13.27	-0.11	9.58	7.04

- 12 healthy adults males; all CYP2D6 EMs
- Measurements taken at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 hours postdose

Kelly et al. Hemodynamic effects of acute administration of atomoxetine and methylphenidate. J. Clin. Pharmacol. 45(7): 851-855 (2005) and data on file at Eli Lilly and Company.

Mean Changes from Baseline to Endpoint in Blood Pressure and Heart Rate During Atomoxetine Treatment in CYP2D6 PMs and EMs (Child/Adolescent Clinical Trials)

- ***No placebo subtraction***

	Extensive CYP2D6 Metabolizers		Poor CYP2D6 Metabolizers	
	N	Mean Change at Endpoint	N	Mean Change at Endpoint
Heart rate (bpm)				
>1.2 mg/kg/day	2483	6.0	167	10.3
Any dose	2863	5.8	226	9.7
Systolic BP (mmHg)				
>1.2 mg/kg/day	2486	3.2	167	3.2
Any dose	2866	3.1	226	3.5
Diastolic BP (mmHg)				
>1.2 mg/kg/day	2486	2.6	167	4.6
Any dose	2866	2.6	226	4.2

Michelson et al. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. J. Am. Acad. Child. Adolesc. Psychiatry 46(2): 242-251 (2007).

Mean Changes from Baseline to Endpoint in Blood Pressure and Heart Rate During Atomoxetine or Methylphenidate Treatment (Clinical Trial)

- ***No placebo subtraction***

	Atomoxetine N=180	Methylphenidate N=40
Heart rate (bpm)	6.14	5.65
Systolic BP (mmHg)	10.68	8.96
Diastolic BP (mmHg)	9.36	8.80

- Up to 10 weeks of open-label treatment
  Atomoxetine: CYP2D6 PMs: 0.2-1.0 mg/kg/day BID
  CYP2D6 EMs: 0.2-2.0 mg/kg/day BID
  mean final dose: PMs: 0.48 mg/kg/day; EMs: 1.40 mg/kg/day
  Methylphenidate: 5-60 mg/day, QD to TID
  mean final dose: 31.3 mg/day

Kratochivil et al. Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. J. Am. Child. Adolesc. Psychiatry 41(7): 776-784 (2002).

Summary

- In 2 intensive hemodynamic evaluations, atomoxetine influence was greater than observed in clinical trials
  - Exposure to “maximum doses”
  - Intensive monitoring (compliance)
  - Quality of measurements
  - Habituation in longer term clinical trials
  - Intrinsic differences (age, pathology)
- In 1 direct, intensive comparison, influence of methylphenidate was greater than that of atomoxetine
  - Influence of methylphenidate greater than reported in clinical trials (Stiefel G, Besag FM. Cardiovascular effects of methylphenidate, amphetamines and atomoxetine in the treatment of attention-deficit hyperactivity disorder. Drug Safety 33(10): 821-842 [2010])
- Such intensive studies cannot be performed in children