Levomilnacipran Inhibits Both Norepinephrine and Serotonin Reuptake Across the Clinical Dose Range

Joann O'Connor | Laishun Chen | Carl Gommoll | Pradeep Banerjee | Stephen Zukin

Forest Research Institute, Jersey City, NJ, USA

INTRODUCTION

Dysfunction of the norepinephrine (NE) and serotonin (5-HT) systems is thought to play a central role in the etiology and pathophysiology of major depressive disorder (MDD). Some symptoms of depression, such as anxiety, agitation, and irritability, have been more closely associated with 5-HT while other depressive symptoms, such as fatigue, lack of motivation, and decreased concentration, appear to be more strongly related to NE.[1] Effective treatment options for MDD include the serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine, venlafaxine, and desvenlafaxine. These compounds all show greater potency in vitro for inhibiting reuptake of 5-HT relative to NE and studies have suggested that duloxetine and venlafaxine may only inhibit NE reuptake in patients at higher doses.[2-4]

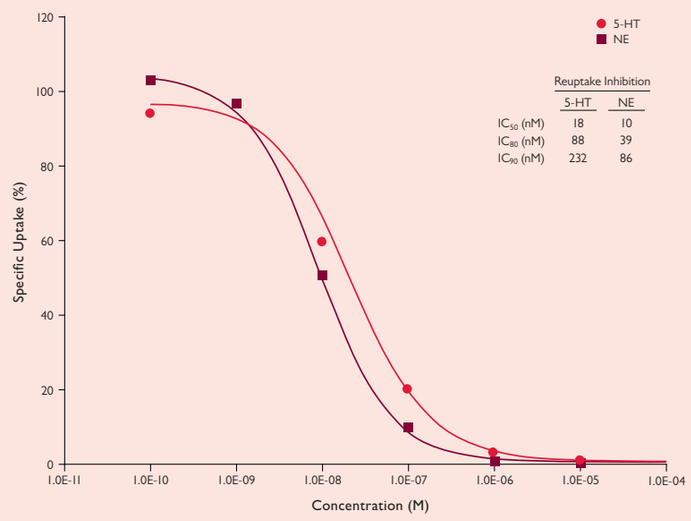
In contrast, levomilnacipran, a potent and selective SNRI, shows greater potency in vitro for the inhibition of NE reuptake relative to 5-HT reuptake.[5] Levomilnacipran extended-release (ER) was recently approved for the treatment of MDD in adults. The efficacy and safety of levomilnacipran ER was established in 3 phase III studies.[6-8] Long-term safety was supported by a 48-week open label study.[9]

The objective of this study was to characterize the pharmacokinetic (PK) profile of levomilnacipran ER 40, 80, and 120 mg/day in patients with MDD and use the PK data to estimate NE and 5-HT reuptake inhibition over the levomilnacipran ER dose range.

BACKGROUND

- The pharmacological profile of levomilnacipran was previously evaluated by Auclair et al[5]
- These raw data were reanalyzed using the mean data from the 3 experiments[5] and inhibition dose curves were plotted (Figure 1)
  - Levomilnacipran showed greater potency for inhibiting NE reuptake compared with 5-HT reuptake, with IC_{50} values of 10 nM and 18 nM, respectively
  - In vitro, the levomilnacipran IC_{80} and IC_{90} values were estimated to be 39 nM and 86 nM, respectively, for the NE reuptake transporter, and 88 nM and 232 nM, respectively, for the 5-HT reuptake transporter

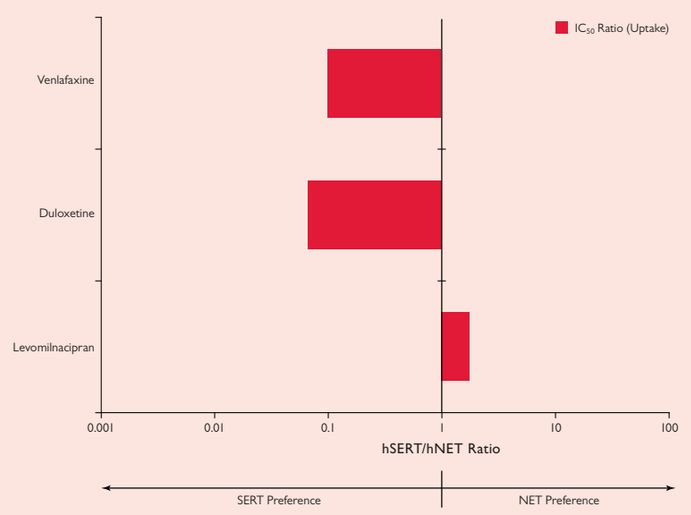
Figure 1. In Vitro 5-HT and NE Reuptake Inhibitory Profiles of Levomilnacipran[a]



[a]Curves based on raw in vitro data from Auclair et al.[5]
In vitro inhibition assays were performed using CHO cells stably expressing transfected hSERT or hNET as previously described.[5] The raw in vitro data were curve fitted to construct inhibition curves using SigmaPlot (Ver 12.0) and the equation: $y = min + (max\text{-}min)/(1 + [x/IC_{50}]^{\gamma})$ where x = levomilnacipran concentration, y = % of remaining actity, min = minimal remaining activity; max = maximal remaining activity, IC_{50} = concentration at 50% inhibition, and γ = Hill slope. Concentrations at IC_{80} and IC_{90} were calculated based on parameters of the equation derived from the fitting.

- While levomilnacipran, duloxetine, and venlafaxine inhibit both 5-HT and NE transport, the different pharmacological profiles of these compounds might have clinical significance
- Venlafaxine and duloxetine showed higher potency for inhibiting the serotonin transporter (SERT) versus the norepinephrine transporter (NET); in contrast levomilnacipran shows preference for inhibiting NET relative to SERT (Figure 2)

Figure 2. Comparison of SNRIs at Serotonin Versus Norepinephrine Transporters[a]



[a]Adapted from Auclair et al.[5]
In vitro inhibition assays were performed using CHO cells stably expressing transfected hSERT or hNET as previously described.[5]
hSERT indicates human serotonin transporter; hNET, human norepinephrine transporter.

METHODS

Pharmacokinetic Analyses

- PK data were collected from adult patients with MDD who participated in a positive 8-week placebo-controlled, fixed-dosed trial of levomilnacipran ER 40, 80, and 120 mg/day[6]
- Approximately 15% of patients in each levomilnacipran ER dose group consented to give serial blood samples after the first 4 weeks of double-blind treatment
- Blood samples were collected predose and at 2, 4, 6, 8, 12, and 24 hours postdose
- Plasma samples were analyzed using a validated liquid chromatography-tandem mass spectrometry method; PK analysis was performed using Phoenix WinNonlin (Ver 6.1)
- Unbound plasma concentrations were estimated based on the previously determined levomilnacipran plasma protein binding value of 22%[10]

Estimation of Clinical NE and 5-HT Reuptake Inhibition

- Conventional plasma concentration units (ng/mL) of levomilnacipran were converted to molar concentration (nM) units to allow for comparison to in vitro NE and 5-HT reuptake inhibition results
- Unbound plasma concentrations were obtained over a 24-hour period from MDD patients receiving 40-, 80-, or 120-mg doses of levomilnacipran ER and plotted against time
- To evaluate how these plasma concentrations compared to concentrations that inhibited NE and 5-HT reuptake in vitro (human recombinant transporters), the recalculated IC_{50}, IC_{80}, and IC_{90} values from the Auclair et al study published in 2013[5] (see background) were superimposed on the graph

RESULTS

Pharmacokinetic Profile

- The mean maximum plasma concentrations (C_{max}) were 92.8, 180.4 , and 297.2 ng/mLfor the 40-, 80-, and 120-mg doses, respectively (Table 1)
- The mean time to maximum observed plasma concentration (T_{max}) was 6 hours for all 3 doses
- The mean areas under the plasma concentration-time curves from zero to 24 hours ($AUC_{0\text{-}\tau}$) were 1519.8, 2934.9, and 4798.5 h*ng/mL for levomilnacipran ER 40, 80, and 120 mg/day, respectively
- The mean trough plasma concentrations (C_{min}) at steady state were 28.8, 52.3, and 90.7 ng/mL for levomilnacipran ER 40, 80, and 120 mg/day, respectively
  - These values are equivalent to 109.1, 198.1, and 343.6 nM, respectively

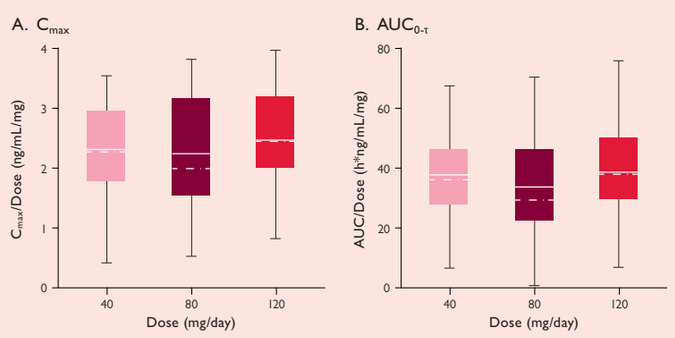
Table 1. Pharmacokinetic Parameters of Levomilnacipran ER Following Multiple-Dose Administration[a]

PK Parameter	40 mg (n=37) Mean ± SD	80 mg (n=31) Mean ± SD	120 mg (n=32) Mean ± SD
C_{max}, ng/mL	92.8 ± 29.3	180.4 ± 71.4	297.2 ± 98.1
T_{max}, hours[b]	6 (4, 24)	6 (2, 24)	6 (4, 10)
$AUC_{0\text{-}t}$, h*ng/mL	1519.8 ± 533.3	2722.2 ± 1327.4	4675.9 ± 1758.5
$AUC_{0\text{-}\tau}$, h*ng/mL	1519.8 ± 533.3	2934.9 ± 1171.9[c]	4798.5 ± 1642.6[d]
C_{min}, ng/mL	28.8 ± 17.8	52.3 ± 47.7	90.7 ± 56.8
C_{ave}, ng/mL	63.3 ± 22.2	122.3 ± 48.8[c]	199.9 ± 68.4[d]

[a]Patients with a series of plasma samples with evaluable PK parameters were included; [b]median (minimum, maximum); [c]n=28; [d]n=31.
$AUC_{0\text{-}t}$ = area under the curve for plasma concentration versus time from time zero to dose-interval time τ; $AUC_{0\text{-}\tau}$ = area under the curve for plasma concentration versus time from time zero to time τ; C_{max} = maximum plasma concentration at steady state; C_{min} = minimum plasma concentration at steady state; C_{ave} = average plasma concentration at steady state; PK = pharmacokinetic; T_{max} = time of maximum plasma concentration.

- Similar dose-normalized C_{max} and $AUC_{0\text{-}\tau}$ values for levomilnacipran ER 40, 80, and 120 mg indicated that levomilnacipran steady state PK was linear and dose proportional following multiple-dose oral administration of levomilnacipran ER in the dose range of 40-120 mg/day (Figure 3)

Figure 3. Dose-Normalized Maximum Plasma Concentration (C_{max}) and Area Under the Curve ($AUC_{0\text{-}\tau}$) Values



Whiskers represent data within 1.5 x the interquartile range (IQR) of the lower and upper quartile. Solid and dashed lines indicate mean and median values, respectively.

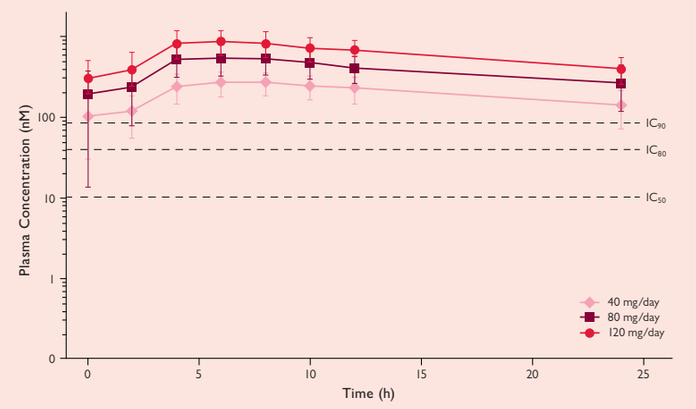
CONCLUSIONS

- C_{max} and AUC of levomilnacipran are linear and proportional in the approved dose range of 40-120 mg/day; the median T_{max} is 6 hours in patients with MDD
- In plasma, once-daily levomilnacipran ER administration is expected to result in concentrations that will inhibit NE and 5-HT reuptake more than 90% and 80%, respectively, across the 24-hour dosing interval and approved dose range
- These data suggest that the clinical effects of NE and 5-HT reuptake inhibition may be achieved at all 3 clinically approved levomilnacipran ER doses (40, 80, 120 mg/day)
- Inhibition of both NE and 5-HT across the approved dose range may differentiate levomilnacipran ER from the SNRIs duloxetine and venlafaxine, which may only show clinically meaningful NE reuptake inhibition at higher doses

Estimated NE and 5-HT Reuptake Inhibition

- Following multiple-dose administration, the average unbound plasma concentrations for levomilnacipran that were reached in MDD patients treated with levomilnacipran ER 40, 80, or 120 mg/day exceeded the concentration that showed 90% inhibition of NE (Figure 4)
  - Mean unbound levomilnacipran levels exceeded the estimated IC_{90} values for NE reuptake inhibition for the entire 24-hour dosing period

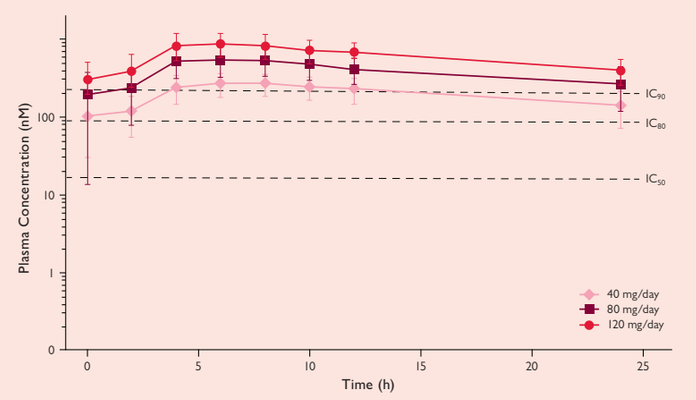
Figure 4. Levomilnacipran Plasma Unbound Concentration Compared to In Vitro NE Reuptake Inhibition (IC) Values[a]



[a]NE reuptake inhibition was estimated using in vitro data (CHO cells expressing hNET) from Auclair et al.[5]

- For all 3 levomilnacipran ER doses, levomilnacipran unbound plasma levels exceeded the estimated IC_{80} values for 5-HT reuptake inhibition following multiple-dose administration (Figure 5)
  - The plasma levels necessary for 80% 5-HT reuptake inhibition were maintained for the entire 24-hour dosing period

Figure 5. Levomilnacipran Plasma Unbound Concentration Compared With In Vitro 5-HT Reuptake Inhibition Values[a]



[a]5-HT reuptake inhibition was estimated using in vitro data (CHO cells expressing hSERT) from Auclair et al.[5]

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Levomilnacipran inhibits both norepinephrine and serotonin reuptake across the clinical dose range

J. O'Connor[1], L. Chen[1], C. Gommoll[1], P. Banerjee[1], S. Zukin[1]

[1]Forest Research Institute, New Jersey, USA

Introduction: Serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors (SNRIs) are generally considered to be first-line treatment options in patients with major depressive disorder. Levomilnacipran extended-release (ER) is a potent and selective SNRI that has been approved for the treatment of major depressive disorder in adults. In vitro, levomilnacipran has been shown to have greater potency for inhibition of NE relative to 5-HT reuptake [1]. Using data from a phase 3 clinical trial, the pharmacokinetic (PK) profile of levomilnacipran ER 40mg/day, 80mg/day, and 120mg/day was evaluated, with analyses conducted to estimate 5-HT and NE reuptake inhibition over the levomilnacipran ER dose range.

Methods: Data were from adult patients with major depressive disorder who participated in a positive 8-week, placebo-controlled, fixed-dose trial of levomilnacipran ER 40mg/day, 80mg/day, and 120mg/day (NCT00969709) [2]. Approximately 15% of patients in each levomilnacipran ER dose group consented to give serial blood samples at week 4 of double-blind treatment, which were collected at predose and at 2, 4, 6, 8, 10, 12, and 24 hours postdose. Plasma samples were analyzed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Unbound plasma concentrations were estimated based on the previously determined levomilnacipran plasma protein binding value of 22%. To evaluate the inhibition of 5-HT and NE reuptake over the clinical dose range of levomilnacipran ER, unbound plasma concentrations obtained over a 24-hour period from patients were plotted and compared against in vitro 5-HT and NE reuptake inhibition values previously generated [1] based on IC_{50} equation.

Results: Steady-state PK profiles were linear and dose proportional following oral administration of levomilnacipran ER in the dose range of 40 to 120mg/day. Maximum plasma concentrations (C_{max}) were 92.8ng/mL, 180.4ng/mL, and 297.2ng/mL, for the 40-, 80-, and 120-mg doses, respectively. Time to maximum observed plasma concentration (T_{max}) was 6 hours for all 3 doses. Areas under the plasma concentration-time curves from zero to 24 hours (AUC_{0-T}) were 1519.8, 2934.9, and 4798.5h*ng/mL for levomilnacipran ER 40, 80, and 120mg/day, respectively. Average plasma concentrations at steady state for unbound levomilnacipran were 63.3ng/mL for 40mg/day, 122.3ng/mL for 80mg/day, and 199.9ng/mL for 120mg/day. Population PK modeling revealed that these plasma concentrations for levomilnacipran exceeded the concentration which showed 90% and 80% inhibition of NE and of 5-HT reuptake, respectively, in vitro.

Conclusions: These data from adult patients with major depressive disorder suggest that levomilnacipran ER pharmacokinetics are dose-proportional and that this drug may potently inhibit both NE and 5-HT reuptake at all clinically effective doses. The data also suggest that the clinical benefits of NE and 5-HT reuptake inhibition could potentially be achieved at all 3 clinically approved levomilnacipran ER doses.

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