Clinical doses of atomoxetine significantly occupy both norepinephrine and serotonin transports: Implications on treatment of depression and ADHD.

Ding YS, Naganawa M, Gallezot JD, Nabulsi N, Lin SF, Ropchan J, Weinzimmer DB, McCarthy TJ, Carson RE, Huang Y, Laruelle M.

Department of Diagnostic Radiology, Yale University, New Haven, CT, USA; Department of Psychiatry and Radiology, New York University, New York, NY, USA. Electronic address: yu-shin.ding@nyumc.org.

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BACKGROUND:
Atomoxetine (ATX), a drug for treatment of depression and ADHD, has a high affinity for the norepinephrine transporter (NET); however, our previous study showed it had a blocking effect similar to fluoxetine on binding of [11C]DASB, a selective serotonin transporter (SERT) ligand. Whether the therapeutic effects of ATX are due to inhibition of either or both transporters is not known. Here we report our comparative PET imaging studies with [11C]MRB (a NET ligand) and [11C]AFM (a SERT ligand) to evaluate in vivo IC50 values of ATX in monkeys.

METHODS:
Rhesus monkeys were scanned up to four times with each tracer with up to four doses of ATX. ATX or saline (placebo) infusion began 2h before each PET scan, lasting until the end of the 2-h scan. The final infusion rates were 0.01-0.12mg/kg/h and 0.045-1.054mg/kg/h for the NET and SERT studies, respectively. ATX plasma levels and metabolite- corrected arterial input functions were measured. Distribution volumes (VT) and IC50 values were estimated.

RESULTS:
ATX displayed dose-dependent occupancy on both NET and SERT, with a higher occupancy on NET: IC50 of 31±10 and 99±21ng/mL plasma for NET and SERT, respectively. At a clinically relevant dose (1.0-1.8mg/kg, approx. 300-600ng/mL plasma), ATX would occupy >90% of NET

and >85% of SERT. This extrapolation assumes comparable free fraction of ATX in humans and non-human primates.

CONCLUSION:
Our data suggests that ATX at clinically relevant doses greatly occupies both NET and SERT. Thus, therapeutic modes of ATX action for treatment of depression and ADHD may be more complex than selective blockade of NET.