

Comment on Wheaton 2011 and Lee 2005.

Wheaton P, Mathias JL, Vink R. Impact of Pharmacological Treatments on Cognitive and Behavioral Outcome in the Postacute Stages of Adult Traumatic Brain Injury. A Meta-analysis. J Clin Psychopharmacol 2011;31:745-757.

Lee H, Kim S-W, Kim J-M et al. Comparing effects of methylphenidate, sertraline, and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. Human Psychopharmacol Clin Exp 2005;20:97-104.

Wheaton 2011 concludes that “early treatment with sertraline worsened postconcussion symptoms and cognition” but appropriately qualifies this by stating that “these findings require further evaluation using adequately powered randomized controlled trials to substantiate the findings of this meta-analysis.”

This conclusion is based upon a citation from Lee 2005, which Wheaton interprets as saying “there was a noticeable increase in postconcussion symptoms and a marked decrease in psychomotor speed (motor speed-choice reaction time). Moderate declines were also found in general cognition, cognitive speed, and memory.”

However, Table 2 of Lee reports postconcussion symptoms in terms of the Rivermead scale, for which the sertraline group had a baseline score of 32.0 and a 4 week score of 30.3, an inconsequential decrease, but not a noticeable increase.

Similarly, Table 3 of Lee reports 10 different tests of cognitive function; only one of the 10, the mental arithmetic test, showed a decline; even for this test, the ANOVA showed no significant differences between sertraline, methylphenidate, and placebo. For eight of the other nine cognitive tests, the sertraline group had small but insignificant improvements. In one test, the Total Reaction Time, the sertraline group had a significant improvement between baseline and 4 weeks; the other two groups showed significant improvements on the same test over the same 4 week interval.

For one comparison, the recognition reaction time, Lee reported improvements in all three groups between baseline and 4 weeks; both methylphenidate and placebo were superior to sertraline ($p=.021$ for ANOVA for that comparison).

Because ten cognitive comparisons were made, it would be desirable to have one outcome designated in advance as a primary outcome. However, Lee did not designate which of the ten outcomes was of primary interest. An adjustment of the p value should be strongly considered, since the simultaneous testing of ten null hypotheses may easily produce a single p value less than 0.05 even when all ten null hypotheses are true (the probability of this occurring with ten comparisons is approximately 40%).

Lee reported that methylphenidate was superior to sertraline in ease of morning awakening. This outcome did not change with sertraline. Because methylphenidate is a

stimulant, this is not an unexpected finding, and it is noteworthy that sertraline neither produced neither an improvement nor a worsening of morning wakening.

In summary, Wheaton cited a study of sertraline which does not support a conclusion that sertraline has adverse cognitive effects. Wheaton is correct to await larger randomized and properly conducted clinical trials before conclusions about the effects of sertraline can be drawn.