ELSEVIER

LETTER TO THE EDITOR

Where Do We Go from Here? The Importance of Initial Values

Cognitive status in schizophrenia is now recognized as an important determinant for patient outcome and therefore represents an essential target for remediation (Friedman et al. 1999). In a recent study Friedman et al. (2001) assessed the potential utility of guanfacine, an α_{2A}-noradrenergic agonist, for improving working memory, sustained attention and learning in a group of treated, stable patients with schizophrenia. While there was no *overall* effect of guanfacine on cognitive performance, the authors performed a supplementary analysis on the group of patients stabilized on the atypical neuroleptic risperidone which 'revealed some significant and some trend differences on cognition compared with placebo.' These findings may represent a real benefit in a subgroup of patients, although closer inspection of the data reveals that alternative accounts remain viable.

In the interpretation of psychopharmacological studies of cognition, the influence of baseline performance on subsequent response to a drug challenge has been discussed by a number of authors (Robbins and Sahakian 1979; Kimberg et al. 1997; Mattay et al. 2000; Mehta et al. 2000). Tasks of working memory and executive function may be both impaired (Kimberg et al. 1997) or improved (Kimberg et al. 1997; Mehta et al. 2000) following dopaminergic agonists, dependent on baseline working memory capacity. Using the stimulant, amphetamine, Mattay et al. (2000) demonstrated that such baseline-dependent cognitive effects may be paralleled by changes in brain activity as indexed by functional magnetic resonance imaging BOLD signal. Such effects have been well-characterized, behaviorally, in experimental animals and clearly suggest an inverted U-shaped relationship between dopamine activity and working memory performance (excessive as well as insufficient dopamine stimulation impairs function).

Friedman et al. (2001) present both the baseline and post-treatment data for the schizophrenic patients on risperidone in the figures. Unfortunately it is apparent that, for the groups of patients subsequently receiving four weeks guanfacine or placebo, baseline performance is not equivalent. While guanfacine may genuinely improve performance of some cognitive tasks, at least in normal volunteers (Jakala et al. 1999a,b), one cannot discount the alternative accounts of baseline-dependent drug effects, formulated as regression to the mean or the law of initial value (Wilder 1958). Indeed, the baseline performance of subjects given guanfacine or placebo was not compared. Moreover, although the seemingly correct use of non-parametric statistics is acknowledged, the test-retest reliability of the working memory task in patients with schizophrenia may also be questionable based upon the apparent impairment in those receiving placebo. While it remains possible that patients with poorer cognitive function may be particularly amenable to the effects of putative cognitive enhancers such as guanfacine, the trivial explanation of patients initially performing badly improving on the second testing session, and patients performing well subsequently performing less well, cannot be overlooked for the data as presented.

In order to fully evaluate the efficacy of putative modulators of cognitive function it is crucial not only to accurately monitor the effect of the agent itself, but also to place this in the context of the initial state of the pa-

From the Imperial College School of Medicine, PET Psychiatry, Cyclotron Building, Hammersmith Hospital Du Cane Road, London, UK.

Address correspondence to: Mitul A. Mehta , Ph.D., Hammersmith Hospital, PET Psychiatry, Imperial College School of Medicine, Du Cane Road, London W12 0NN, UK. Tel.: +44 (0) 20 83833703; E-mail: mitul.mehta2@ic.ac.uk

Received October 31, 2001; accepted February 27, 2002.

Online publication: 4/23/02 at www.acnp.org/citations/Npp042302264.

Letter to Neuropsychopharmacology submitted 11/09/01.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/02/$–see front matter
PII S0893-133X(02)00359-7

tients or experimental animals. When you're at the top, the only way is down, but when you're at the bottom the only way is up.

Mitul A. Mehta, M.A., Ph.D.

REFERENCES

Friedman JI, Temporini H, Davis KL (1999): Pharmacologic strategies for augmenting cognitive performance in schizophrenia. Biol Psychiatry 45:1–16

Friedman JI, Adler DN, Temporini HD, Kemether E, Harvey PD, White L, Parrella M, Davis KL (2001): Guanfacine treatment of cognitive impairment in schizophrenia. Neuropsychopharmacology 25:402–409

Jakala P, Riekkinen M, Sirvio J, Koivisto E, Kejonen K, Vanhanen M, Riekkinen P Jr (1999a): Guanfacine, but not clonidine, improves planning and working memory performance in humans. Neuropsychopharmacology 20:460–470

Jakala P, Sirvio J, Riekkinen M, Koivisto E, Kejonen K, Vanhanen M, Riekkinen P (1999b): Guanfacine and clonidine, alpha 2-agonists, improve paired associates learning, but not delayed matching to sample, in humans. Neuropsychopharmacology 20:119–130

Kimberg DY, D'Esposito M, Farah MJ (1997): Effects of bromocriptine on human subjects depends on working memory capacity. Neuroreport 8:3581–3585

Mattay VS, Callicott JH, Bertolino A, Heaton I, Frank JA, Coppola R, Berman KF, Goldberg TE, Weinberger DR (2000): Effects of dextroamphetamine on cognitive performance and cortical activation. Neuroimage 12:268–275

Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW (2000): Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. J Neurosci 20:RC65:1–6

Robbins TW, Sahakian BJ (1979): 'Paradoxical' effects of psychomotor stimulant drugs in hyperactive children from the standpoint of behavioural pharmacology. Neuropharmacology 18:931–950

Wilder J (1958): Modern psychophysiology and the Law of Initial Value. Am J Psychother 12:199–221