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Psychopharmacology: concepts and opinions about the use of stimulant medications

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This 'perspective piece' on the topic of psychopharmacology was requested to be opinion-driven and conceptual in nature, rather than a systematic review or a state-of-the-science article. Recently we (Volkow & Swanson, 2008a) adopted a broad approach to address multiple classes of psychotropic medication used to treat children (stimulants, anti-depressants, and anti-psychotics). We provided examples from traditional clinical pharmacology to discuss their pharamacokinetic (PK) and pharmacodynamic (PD) properties, as well as examples from modern positron emission tomography (PET) brain imaging to characterize the time course of drug effects at the primary cellular sites of action in the brain (transporters, enzymes, and receptors). Rather than repeat this broad approach here, we will provide a narrow, opinion-driven, and conceptual review of one of these classes – stimulant medication – that has been used primarily for the treatment of children with attention deficit hyperactivity disorder (ADHD) and hyperkinetic disorder (HKD) and recently has shown dramatic increases (see Swanson & Volkow, 2008) for the treatment of adolescents and adults. To narrow the scope further, we will focus on established concepts that have been challenged in the literature over the past decade (from 1998 to 2008). As requested, we will focus on personal experiences in research related to these concepts to highlight the historical context and some changes in clinical psychopharmacology over the past decade.

The literature on effects of the stimulant medications amphetamine (AMP) and methylphenidate (MPH) for the treatment of ADHD and HKD is enormous and increasing. However, the fundamental clinical effects of AMP were well described initially by Bradley (1937, 1950) over a half century ago and later by many investigators (including by Weiss, Werry, Minde, Douglas, & Sykes, 1968 in this journal), and the fundamental behavioral and cognitive effects of MPH were described initially by Conners and Eisenberg (1963) over 40 years ago and later by many investigators including by Taylor et al. (1977) and in this journal by Douglas et al. (1986).

Many reviews have been published to summarize the plethora of studies that followed, including influential early reviews in this journal (see Barkley, 1977) and from the European perspective by Taylor (1979) and in this journal by Bramble (2003). All seem to reach about the same basic conclusions about the effects of AMP and MPH that were reported in these initial studies. Fifteen years ago these were summarized by Swanson et al. (1993) in a 'review of reviews' that suggested what should be expected (e.g., short-term reduction in symptoms of ADHD and associated features of opposition and aggression) and what should not be expected (long-term benefits, absence of side effects, paradoxical response, large effect on higher-order processes). Almost a decade later, this was reinforced by Conners (2002), who concluded that the 'effects of stimulants are consistent over time despite changes in diagnosis,

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assessment instrument, and research methodology' (p. S29). So, what new concepts and controversial questions will be addressed here?

Over the past decade there have been some major changes in how the stimulants are used in clinical practice, as well as some major controversies about the fundamental pharmacological and neurochemical processes underlying the action of stimulant medications. For our opinion-driven article we selected five controversial questions to address: (1) How has clinical pharmacology been used to direct major changes in clinical practice? (2) How have new findings from PET imaging studies changed the understanding of the neural effects of stimulant medications and the brain-basis for ADHD? (3) How have long-term outcomes in large-scale clinical trials changed the rationale for treatment with stimulant medications? (4) How has the continued increase in use of stimulants for treatment altered concern about misuse of stimulant medication? (5) How has industry-sponsored research altered the clinical practice of treatment of individuals with stimulant medication?

After addressing these five concepts, we will update expectations about the use of stimulant medications in 2008, discuss the impact of current expectations of the rationale for and clinical practice of using stimulant medications in the treatment of ADHD and HKD, and offer some conclusions based on personal experiences in these areas of research on psychopharmacology.

Controversial concepts and questions

1. How has clinical pharmacology been used to direct major changes in clinical practice?

Changes have occurred in clinical practice since the beginning. The initial clinical practice described by Bradley in 1937 was based on the use of the racemic formulation of AMP (Benzedrine®), which was marketed by Smith, Kline and French in 1936, but by 1950 this shifted to the use of the pure d-isomer of AMP (Dexedrine®) that could be used at lower doses, which was marketed in 1949. By the 1970s, clinical practice had shifted again to the use of a different drug, MPH (Ritalin®), which was developed by CIBA pharmaceutical and received FDA approval in 1960. In 1994, there was an attempt to revive of use of AMP, but this was not successful initially. Richwood Pharmaceuticals tried to market a formulation of AMP developed by Rexar Pharmaceuticals and approved for appetite control in 1960 (Obetrol®, a racemic 75:25 mixture of the d-AMP and l-AMP optical isomers), with a new name (Adderall®). One of the claims was that Adderall® was a unique alternative and long-acting stimulant that could be given once a day and thus avoid in-school dosing (see full page advertisement in the *Journal of the American Academy of Child and Adolescent Psychiatry*, November, 1994). The evidence for this was apparently based on 'some physician's testimony as to special benefit in a segment of ADHD patients' (see FDA Minutes of Meeting, NDA 11–522, 1995), which was challenged by the FDA. An earlier FDA review (see Federal Register, 1973) found insufficient evidence of efficacy and safety of this drug despite the approval before modern guidelines were in place. However, after negotiation with the FDA, Richwood Pharmaceutical received re-approval in 1996 to market Adderall® for the treatment of ADHD, even though there were no controlled trials of the effects on children with ADHD.

This called for clinical pharmacological studies to document under double-blind conditions the PK and PD effects of Adderall®. Richwood Pharmaceuticals funded the first controlled studies, which utilized the laboratory school paradigm and surrogate measures of response to compare the duration of action of immediate release (IR) formulations of AMP (Adderall®) and MPH (Ritalin®) in small groups of children with ADHD. One of these studies confirmed the claim of equal efficacy (maximum effect after an acute dose) and different PD half-lives for Adderall® (6 hours) and Ritalin® (4 hours) (Swanson et al., 1998). The other with just 21 children confirmed equivalence of efficacy of comparable multiple dose regimes for IR formulations with different PD half-lives (i.e., BID Adderall® and TID Ritalin® regimes)

(Pelham et al., 1999). Additional controlled research in naturalistic settings of the home and school confirmed these laboratory studies. As shown in Figure 1a, there was a dramatic increase in prescriptions for IR AMP starting in 1998 that by 2000 remarkably equaled the number of prescriptions for IR MPH. In 2000, Richwood Pharmaceuticals was acquired by Shire Pharmaceuticals, which had a larger sales force and increased the marketing of Adderall®.

The second major change in clinical practice was a shift from IR to controlled release (CR) formulations. One common limitation of Adderall® and Ritalin® was the relatively short duration of action of these IR formulations that required multiple doses to maintain full efficacy across the day. In the 1980s, first-generation CR formulations of AMP (Dexedrine Spansules®) and MPH (Ritalin SR®) were available, but they were considered to have lower efficacy than multiple-dose regimes of the IR formulations and thus were not widely adopted in clinical practice. The consensus opinion was that the stimulant drugs required bolus doses and a PK profile with peaks and valleys to produce and maintain clinical efficacy, which implied an inherent limitation on CR formulations.

This also called for studies based on principles and techniques from clinical pharmacology. In a series of small studies funded by Alza Pharmaceuticals, Swanson et al. (1999) tested the bolus-dose assumption using the 'sipping study' methodology in a small proof of concept study to consider another possible explanation for reduced efficacy of CR formulations – acute tolerance to stimulant medication. A laboratory school study of 29 children with ADHD showed that a zero-order smooth (flat) drug delivery profile was insufficient to maintain efficacy across the day compared to the standard BID regime of IR MPH, but that a first-order smooth (ascending) PK profile without a bolus could achieve the full efficacy of the bolus dose regime. PK/PD modeling (see Levy, 1994; Park et al., 1998) suggested that acute tolerance to MPH could account for this pattern of PD effects. This discovery led to the design of a new commercial product (Concerta®) based on the osmotic release oral system (OROSR), which was modified to achieve the proposed optimum first-order (ascending) drug delivery profile. Concerta® was tested in proof of product studies in the laboratory classroom to document onset and duration of efficacy (see Pelham et al., 2002; Swanson et al., 2003). This was followed by typical multi-site clinical trials with much larger groups of subjects (see Swanson et al., 2000; Wolraich et al., 2001) considered necessary for submission to the FDA in order to document efficacy and safety and gain approval, which was granted in 2000. As shown in Figure 1b, Concerta® had almost immediate acceptance in clinical practice when it was introduced and marketed in 2000. Prescriptions for CR MPH starting increasing then, and by 2002 the use of CR MPH virtually replaced IR MPH in clinical practice. In 2002, Alza Pharmaceuticals was acquired by Johnson & Johnson, which had a larger sales force and increased the marketing of Concerta®.

To maintain competitiveness in the rapidly increasing market for stimulant drugs, Shire Pharmaceutical initiated a drug development program for CR AMP to match the predominant clinical regime of IR AMP (i.e., BID doses of Adderall®) and achieve full efficacy across the day with once-a-day administration. PK studies in adults (see Tulloch et al., 2002) and children (see Greenhill et al., 2003) were conducted to guide this development, which revealed a 6-hour PK half-life of a single dose of IR AMP and an ascending drug delivery profile associated with the BID regime of Adderall® with the doses given 4 hours apart. A dual-beaded drug delivery system was designed to match this ascending drug delivery profile, which was developed as a CR formulation called Adderall XR®. Proof-of-product PK/PD studies confirmed efficacy and duration of action (see McCracken et al., 2003). Upon approval granted by the FDA in 2002, Adderall XR® also gained almost immediate acceptance in clinical practice, as reflected by the rapid increase in prescriptions shown in Figure 1b.

In summary, two major changes in clinical practice occurred over the past decade in the USA (see Figure 1): the dramatic revival of AMP starting in 1998 and widespread acceptance of second-generation CR formulations of MPH and AMP starting in 2000. Both of these changes were stimulated by small studies based on principles of clinical pharmacology, with the latter based on PK/PD modeling and the hypothesis that predicted that smooth ascending PK profiles for once-a-day CR formulations would counteract acute tolerance and maintain full efficacy across the day.

2. How have new findings from PET imaging changed the understanding of brain-basis for ADHD and the neural effects of stimulant medications?

One of the first biochemical theories of ADHD was based on speculation about the neurochemical effects of the stimulants that produced rapid reduction of symptoms. Wender (1971) proposed the catecholamine deficit theory based in part on the belief that stimulants were catecholamine agonists that produced enhancement of NE and DA signals in the brain (see Solanto, 1998 for the history and early elaborations of this biochemical theory).

One question about the neural mechanism of action of MPH revolved around its similarity to cocaine in site and primary mechanism of action, blockade of dopamine transporters (DAT) in the striatum, but without similar euphoric effects. The early studies by Volkow et al. (1995) clarified this by using PET imaging with radiolabeled MPH to document the PK properties of the drug in the human brain. MPH had a much longer brain PK half-life than cocaine, which resulted in persistence of high brain levels of MPH and thus prolonged high exposure after the peak concentration was achieved. Apparently this produced acute tolerance to the brain levels of MPH that initially produced euphoric effects after intravenous dosing. However, questions remained about oral doses of MPH, which historically had been considered to produce a weak stimulant effect, which was assumed to be because rapid peripheral metabolism prevented high brain concentrations of the drug. Volkow et al. (1998, 2002) performed PET studies to estimate the neural effects of oral MPH doses on occupancy of DAT, and documented that on the average 80% of transporters in the striatum were blocked in adults by oral dose less than 1.0 mg/kg. This level of DAT blockade by an oral dose in the clinical range was as great as for intravenous doses of MPH or cocaine. This supported the hypothesis that differences in the euphoric effects of these two drugs were due to differences in their brain PK properties (and the presence of acute tolerance related to the extended presence of high concentrations of MPH in the brain), rather than to low concentrations of MPH at the neural site of action.

PET methods have also been used to investigate possible biological markers for ADHD. An exceedingly influential study by Dougherty et al. (1999) was based on the use of Single Photon Emission Computed Tomography (SPECT), a low resolution alternative to PET, and a new radioligand (iodine-23-labeled altropane) to estimate the density of DAT in the basal ganglia of the brain. A study of 6 adults with ADHD suggested that DAT density was 70% higher than expected by historical norms for the SPECT-altropane method. Some studies by another group have partially replicated the effect in sub-groups of ADHD subjects with different SPECT methods (see Krause et al., 2000). This theory was appealing since high DAT density could account for an ADHD-related DA deficit (i.e., this would produce an increased reuptake of DA released into the synapse), as well as the beneficial response to MPH (i.e., the blockade of DAT would reduce DA uptake and act to correct the DA deficit).

The hypothesis of high DAT density as a brain-basis of ADHD was accepted for over a decade, and is now typically cited as one of the primary biological bases of ADHD. To test this hypothesis, Volkow et al. (2007a) evaluated a larger sample (20 stimulant-naïve adults with ADHD and 25 controls matches for sex and ethnicity) and a more sensitive method of estimating DAT density (using PET rather than SPECT and radiolabeled cocaine rather than

altropane as the ligand). Surprisingly, this study was unable to document lower DAT density in the caudate nucleus or in any basal ganglia region, and in fact observed a trend in the opposite direction. As shown in Figure 2, some of the other subsequent studies (see Volkow et al., 2007 for specific references) using PET methods with higher resolution and larger samples of ADHD and control subjects have also reported failure to replicate the finding of dramatically increased DAT density associated with ADHD.

Based on this selected literature review, we believe that modern PET studies have confirmed the DA-agonist theory of stimulant drugs and have challenged the DAT-density theory of the brain-basis of ADHD. The recent findings from these studies are not universally accepted, so references to the old and long-accepted theories still permeate the literature.

3. How have long-term outcomes in large-scale clinical trials changed the rationale for treatment with stimulant medications?

Despite extensive and accumulating evidence of short-term efficacy of stimulant medication, in 1990 there was a glaring lack of evidence documenting long-term benefits. Several early follow-up studies in the literature suggested that clinical effectiveness could be maintained for years (see Satterfield et al., 2007 for a review), but controlled studies had not been conducted to provide solid evidence of long-term benefit. The Multimodal Treatment study of ADHD (MTA) was initiated in 1993 to evaluate the long-term effects of treatments using the 'gold standard' for evidence-based medicine – a randomized clinical trial (RCT) – to contrast the long-term effects of state-of-the-art pharmacological treatment (MedMgt), psychosocial treatment (Beh), and the combination of these two treatment modalities (Comb). As with most RCTs, relative rather than absolute effects were evaluated by comparing outcomes of these treatments to each other, and (in lieu of a no-treatment control group) to treatment-as-usual in the community (CC). After a 14-month treatment-by-protocol phase, the MTA became an observational follow-up that is still in progress. Elsewhere, the MTA Group has provided summaries and detailed accounts of the main findings, interpretations, and qualifications from the 14-month, 24-month, and 36-month assessments of outcomes (see Arnold et al., 2008; Swanson et al., 2008a, 2008b), so only a brief summary will be presented here. Despite initial evidence of long-term relative benefits over the first two years of treatment, when the definition of long-term was extended to 3 years, the secondary analyses of the MTA follow-up were not able to document any long-term relative benefits of prior or current treatment with stimulant medication. However, post-hoc analyses of growth in MTA revised the once-discredited (see Spencer et al., 1996) hypothesis of stimulant-related growth suppression. By the third year of the study when the participants were between the ages of 10 and 12 years of age, an accumulated reduction in height gain of about 2 cm and a reduction in weight gain by about 2 kg was observed in the newly treated subgroups compared to the subgroup of cases never treated with stimulant medication. The clinical significance of this finding has been questioned by some (see Faraone et al., 2008).

One of the greatest concerns about the long-term clinical use of stimulant medication in childhood has been the possibility that this might increase the risk for drug abuse (see Volkow & Swanson, 2003). However, over the past decade, the opposite was suggested, with claims that childhood treatment with stimulant medication decreased risk (see Wilens et al., 2003). In the 36-month follow-up of the MTA, this hypothesis was evaluated (see Molina et al., 2007). Increased substance use in the ADHD group compared to a non-ADHD classmate control group was documented, but this emergence of early substance use in the ADHD group was not significantly reduced by treatment with stimulant medication. Also, recent publications of long-term follow-up of cohorts that were included in the Wilens et al. (2003) review suggest that by adulthood there was no evidence of the long-term effects of childhood treatment with

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