International Journal of Neuropsychopharmacology (2002), 5, 121—129. Copyright © 2002 CINP
DOI: 10.1017/S1461145702002845

ARTICLE

Efficacy of Adderall and methylphenidate in attention deficit hyperactivity disorder: a drug—placebo and drug—drug response curve analysis of a naturalistic study

Stephen V. Faraone[1,2,3,4], Elizabeth J. Short[5], Joseph Biederman[1,2], Robert L. Findling[5,6], Christine Roe[1] and Michael J. Manos[7]

[1] Pediatric Psychopharmacology Unit of the Child Psychiatry Service, Massachusetts General Hospital, Boston, MA, USA
[2] Harvard Medical School, Boston, MA, USA
[3] Massachusetts Mental Health Center, Boston, MA, USA
[4] Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA, USA
[5] Case Western Reserve University, Cleveland, OH, USA
[6] University Hospitals of Cleveland, Cleveland, OH, USA
[7] Cleveland Clinic Foundation, Cleveland, OH, USA

Abstract

Stimulant medication has, for many years, been the pharmacological treatment of choice for children and adults with attention deficit hyperactivity disorder (ADHD). Recently, several studies have documented the efficacy of a new stimulant, Adderall. Although these initial studies provide useful information for clinicians treating ADHD children, their method of data presentation has provided limited information about the clinical significance of drug effects. Thus, to address the issue of clinical significance, we completed drug—placebo response curve analyses of a blinded, placebo-controlled study of Adderall and methylphenidate (MPH). Our results show that the efficacy of Adderall and MPH to improve functioning is seen throughout the full range of improvement scores. Both drugs prevent worsening and, for a majority of patients, lead to improvements that are well into the normal range. The analyses also highlight an important subgroup of placebo responders, which suggests that future research should focus on how to predict robust placebo response in ADHD patients.

Received 24 June 2001; Reviewed 5 November 2001; Revised 16 December 2001; Accepted 19 December 2001

Key words: Adderall, ADHD, clinical trial, methylphenidate, placebo.

Introduction

Stimulant medication has, for many years, been the pharmacological treatment of choice for children and adults with attention deficit hyperactivity disorder (ADHD) (Biederman et al., 1997). Recently, several studies have documented the efficacy of a new stimulant, Adderall, which consists of 25 % L-amphetamine and 75 % D-amphetamine in four salts (Manos et al., 1999; Pelham et al., 1999a,b; Pliszka et al., 2000; Swanson et al., 1998). Pharmacodynamic studies suggest that Adderall has a longer duration of action than methylphenidate (MPH) (Swanson et al., 1998). Because MPH is currently the most widely prescribed medication for ADHD, several studies have examined the comparative efficacy of Adderall and MPH (Manos et al., 1999; Pelham et al., 1999a,b; Pliszka et al., 2000).

Using a double-blind, placebo-controlled cross-over design, Pelham et al. (1999a) compared two doses of Adderall with two doses of MPH. Compared with placebo, both drugs led to substantial improvements in negative behaviour, academic productivity and behaviour ratings. Consistent with Adderall's longer duration of action, it was more effective than MPH for outcomes measured 4—5 h after ingestion of the medication. Clinical staff recommendations for continued medication favoured Adderall by a 3:1 margin. Another study by the same group showed that a single morning dose of Adderall produced clinical improvements throughout the school day equivalent to MPH received twice daily (Pelham et al., 1999b).

Manos et al. (1999) used a naturalistic, placebo-controlled design in which youths were assigned to Adderall or MPH by their prescribing physician. This study showed that both medications were superior to

Address for correspondence: Dr S. V. Faraone, Pediatric Psychopharmacology Unit (ACC 725), MGH, 15 Parkman Street, Boston, MA 02114, USA.
Tel.-. (617) 726-1731 Fax: (617) 724-1540
E-mail: sfaraone@hmsharvard.edu

placebo in reducing parent- and teacher-reported symptoms of ADHD. This group also reported that a single dose of Adderall was as effective as two daily doses of MPH.

Pliszka et al. (2000) reported a double-blind, placebo-controlled parallel group comparison of Adderall and MPH. Consistent with prior studies, both medications were superior to placebo in improving parent, teacher and clinician ratings of ADHD and associated behaviours. Compared with MPH, Adderall led to significantly more improvements in teacher and clinician ratings. Adderall-treated subjects were nearly five times more likely than MPH-treated subjects to be adequately treated with a single daily dose.

Taken together, these prior studies clearly show Adderall to be superior to placebo. They further suggest Adderall is at least as effective as MPH and may be more effective for some outcomes. Although these initial studies provide useful information for clinicians treating ADHD children, their method of data presentation has provided limited information about the clinical significance of drug effects. We initially addressed the issue of clinical significance by completing drug—placebo response curve analyses of the data of Pliszka et al. (2000). This method, described by Faraone et al. (2000), is a generalization of receiver operating characteristic (ROC) analysis (McNeil and Hanley, 1984), which has been widely applied to assessing the accuracy of diagnostic tests (Siegel et al., 1989, 1990; Swets and Pickett, 1982). The goal of this method is to answer the following questions about drug—placebo or drug—drug differences that have already been shown to be statistically significant: Is the effect clinically meaningful? What does the effect tell us about individual responses? Is the effect due to symptom improvement, the prevention of worsening or both?

A re-analysis of the data of Pliszka et al. (2000) using drug—placebo response curve methodology showed that the ability of Adderall to improve functioning is seen throughout the full range of improvement scores (Faraone et al., 2001). In contrast, MPH showed a substantial effect for 'mildly' and 'much improved' but not for 'very much improved'. These analyses also show that both Adderall and MPH prevented worsening of symptoms, an effect usually obscured by standard analyses. The present report extends this prior work by applying drug—placebo response curve methodology to the data reported by Manos et al. (1999).

Methods

Subjects

This sample is a subset of a clinic-based population referred for diagnosis and treatment of ADHD to the Paediatric Assessment and Evaluation Service (PAES) of a large, urban, teaching hospital. As a result of the hospital infrastructure, the system caters for managed care patients not requiring immediate intervention. Of the 600 patients referred for evaluation to date, 159 have participated in a medication trial. One hundred and seventeen of the subjects receiving medication were administered MPH (n = 117), with 42 administered Adderall (n = 42). The study was approved by the local Institutional Review Board.

Diagnoses

All children diagnosed with ADHD met full DSM-IV diagnostic criteria for this disorder. The criteria are (1) the presence of at least six symptoms for inattention and/or at least six symptoms for hyperactivity/impulsivity; (2) symptoms significantly interfered with functioning at home and at school as noted during structured or semi-structured clinical interviews with the Computerized Diagnostic Interview for Children (CDISC); (3) symptom severity on broad-band [i.e. Conners' Abbreviated Symptoms Questionnaire (Conners, 1969)] and narrow-band [e.g. ADHD Rating Scale (DuPaul, 1991)] rating scales was at threshold or above (i.e. rated 2 or 3); (4) multiple raters (e.g. parents and teachers) agreed to the presence of the symptoms; and (5) empirical comparison to norms indicated at least a 1.5 s.d. cut-off on at least one rating scale. It should be noted that in identifying the presence of symptoms, behaviours across informants were not pooled observations. Behaviours were only considered significant if two informants agreed to the presence of the symptom on rating scales or in interviews.

Design

Matching procedures

MPH and Adderall protocols were run simultaneously, with medication assigned to subjects based on physicians' discretion and familiarity with the medication. The 42 patients who received Adderall exhausted our sample of children given this medication. We selected 42 subjects from the MPH group (n = 117) who were approximately the same age (± 6 months), and were the same gender as those enrolled in the Adderall group. As described by Manos et al. (1999), the sample was predominantly Caucasian, well educated and without significant comorbid disorders. Sixty percent were older than 9 yr, and 79 % were male and 55 % had combined-type ADHD; the remainder had inattentive type. The MPH and Adderall groups did not differ in clinical or demographic features.

Pharmacological protocol

All subjects in this study were evaluated using a 4-wk double-blind, placebo-controlled protocol. Each child's paediatrician determined whether MPH or Adderall was to be used. Type of medication administered was based on physicians' familiarity with the agent (i.e. often related to the number of times they had previously prescribed the medication), as well as whether they wanted a child to receive a single dose (Adderall) or twice-daily dose (MPH) of medication for treatment of ADHD. This latter decision was usually based on a parent's concern about the child taking medication in school. Fifteen of the Adderall subjects had previously used MPH but were discontinued due to failure to respond (n = 7) or negative side-effects („ = 8). None of the MPH patients had a prior history of using Adderall.

Subjects received each of four MPH (twice-daily) or Adderall (four times daily) dosing schedules in a randomly assigned sequence. Each of the four doses was administered for a 7-d period. Medication was initiated the day after the baseline assessment. The four stimulant drug conditions were as follows: A_p placebo; B_p 5 mg Adderall or 10 mg MPH (low total daily dose); B_2, 10 mg Adderall or 20 mg MPH (moderate total daily dose); B_3, 15 mg Adderall or 30 mg MPH (high total daily dose). Six dose orders were used such that the highest dose (15 mg Adderall) was given only when preceded by the moderate dose (10 mg Adderall). Dose orders were assigned to subjects in a random fashion. The possible dose orders were the following:

$$A_p\text{–}B_p\text{–}B_2\text{–}B_3\ A_p\text{–}B_2\text{–}B_3\text{–}B_1\ B_p\text{–}B_2\text{–}B_3\text{–}A_1$$

$$B_p\text{–}A_p\text{–}B_2\ B_3\ B_2\text{-}B_3\text{–}A_1\text{-}B_1\ B_2\text{–}B_3\text{–}B_p\text{–}A_1$$

Fixed doses (vs. mg/kg) were prescribed because they reflect typical paediatric practice and because MPH dosage has been shown to be independent of body weight (Rapport et al., 1989a,b). Also, fixed doses provide increased flexibility in comparing data sets with previous studies, providing more information about ADHD children's response to stimulants. All MPH, Adderall and placebo dosings were prepared by licensed pharmacists and packaged in white gelatin capsules to avoid detection of placebo or active medicine by taste. Capsules were sealed in individual bottles dated by week to control for accurate dose administration. Parents were given one bottle of capsules every week and were asked to return bottles at the end of the week with unused capsules to insure compliance with the protocol. MPH capsules were given in the morning (08:00 hours) and at noon each day. Adderall capsules were administered in the morning only. While both the clinician and parent knew to which medication condition each child had been assigned, the clinician, teacher, and parent were blind to the weekly dose administered.

Outcome measures

For all of the following outcome measures, we analysed the outcome reported for the 'best dose' of each medication. Best dose was assigned by the consensus of a clinical child psychologist and a board-certified child and adolescent psychiatrist prior to the medication blind being broken.

ADHD Rating Scale (ARS)

The ADHD Rating Scale (DSM-III-R and DSM-IV versions) (DuPaul, 1991, and unpublished observations) comprises items assessing the symptoms of the ADHD diagnostic category. For this study, items on the DSM-III-R version were revised to reflect the new symptom criteria of the DSM-IV. The severity of symptoms is rated on a problem scale of '0 = not at all' to '3 = very much'. The sum of items scored 2 or higher determines whether a child meets the formal diagnostic criteria for ADHD. The ARS has been shown to discriminate ADHD children from learning disabled children and non-learning disabled children, to differentiate children with hyperactivity from children without, and to be sensitive to stimulant drug effects (Barkley et al., 1990).

The Abbreviated Symptoms Questionnaire (ASQ)

The ASQ is a parent and teacher rating form (Conners, 1969). The 10-item rating scale is similar to the ARS in format. That is, parents and teachers rate children's symptoms on a scale of 0—3, with 0 indicating that the symptom is not present at all and 3 indicating that the symptom is very much present. The ASQ is considered to be the gold-standard of rating scales and was included for validation purposes.

Composite ratings

Based on parental report of weekly behaviour problems, the primary clinician rated the child's behaviour at the end of each week on a scale of — 5 (significant deterioration) to +5 (significant improvement). These weekly composite ratings reflected both clinicians' (M. J. M. and R. L. F.) summary based on a review of standardized data, parental report, and anecdotal data.

School Situations Questionnaire—Revised (SSQ—R)

The SSQ—R (DuPaul, unpublished observations) is an 8-item measure assessing specific problems with attention

and concentration at school. Respondents first rate whether a child has problems in a given situation, then rate the severity of that problem from ' 1 = mild' to '9 = severe'. The scale has adequate test—retest reliability and correlates highly with other teacher ratings scales of ADHD symptomatology. The SSQ—R has been found to be sensitive to the effects of stimulant medication interventions (Barkley, 1990) and to discriminate ADHD from non-AD HD children (Barkley, 1990). 'Part scores' used in analyses excluded items for which teacher ratings were consistently unavailable (e.g. 'during movies', 'film-strips', 'on field trips').

Drug—placebo and drug—drug response curve analysis

The rationale and methodology for the method are described in detail by Faraone et al. (2000). The goal of response curve analysis is not to demonstrate statistically significant group differences. Instead, this method provides a means of displaying differences already demonstrated to be statistically significant. Thus, it does not replace a standard statistical analysis but augments that analysis by showing the clinical significance of drug effects.

There are six steps in drawing the curve: (1) choose an outcome variable; (2) for the drug and placebo groups separately, calculate for each observed score the proportion of subjects having that score or a better score; (3) for each observed score, plot the proportions computed in item (2) for the drug group on the vertical axis against the proportions computed for the placebo group on the horizontal axis; (4) connect the plotted points and label those that correspond to the best response, the 25th percentile of response, the median response, the 75th percentile of response and the worst response; and then (5) plot the line of no effect. This is the diagonal line from the [0, 0] point to the [I, I] point. The line of no effect comprises all points for which the proportion of subjects who respond to drug is the same as the proportion who respond to placebo.

The drug—placebo response curve is a graphical method of describing results from a clinical trial, not a statistical test. It is most sensibly used to describe an effect that has been demonstrated with appropriate statistical tools. Nevertheless, the drug—placebo response curve's roots in ROC analysis motivates the computation of one statistic, the area under the curve (AUC). The AUC ranges from 0.5 (when the drug effect equals the placebo effect) to 1.0. The AUC is a useful index of clinical significance because it equals the probability that a randomly selected member of the drug group will have a better result than a randomly selected member of the placebo group (Colditz et al., 1988; Hanley and McNeil, 1982), i.e. the probability that drug will outperform placebo.

Although the drug—placebo response curve was originally developed to assess drug—placebo differences, it can also be used to compare two active drugs by creating a drug—drug response curve. The only difference in this drug—drug response curve is that the vertical axis corresponds to the superior drug and the horizontal axis corresponds to the other drug.

Results

In the original analyses reported by Manos et al. (1999), all of the rating-scale measures showed statistically significant drug—placebo differences for both Adderall and MPH. There were not statistically significant differences between Adderall and MPH. Thus, we created

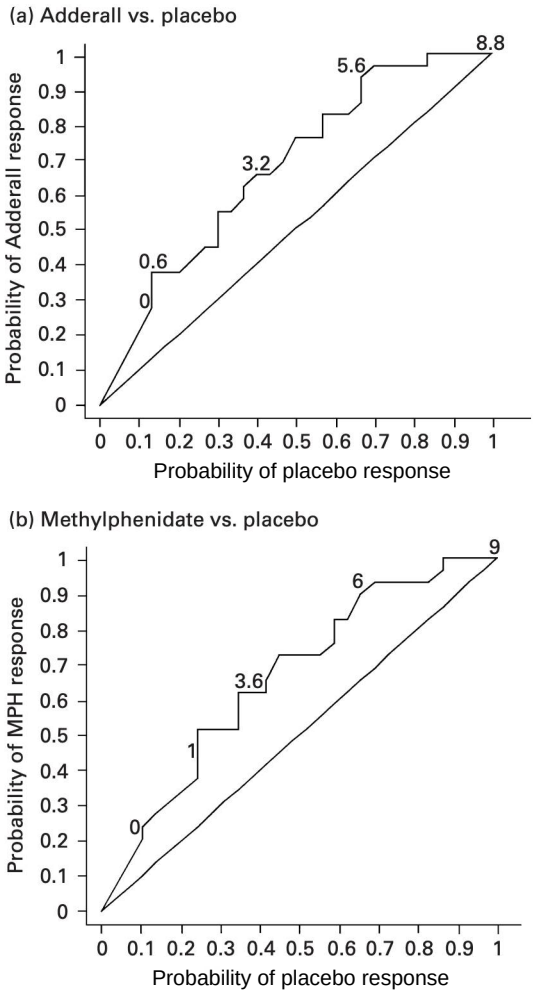

Figure 1. School Situations Questionnaire — Teachers. Possible scores range from 0 (no symptoms) to 9 (severe symptoms).

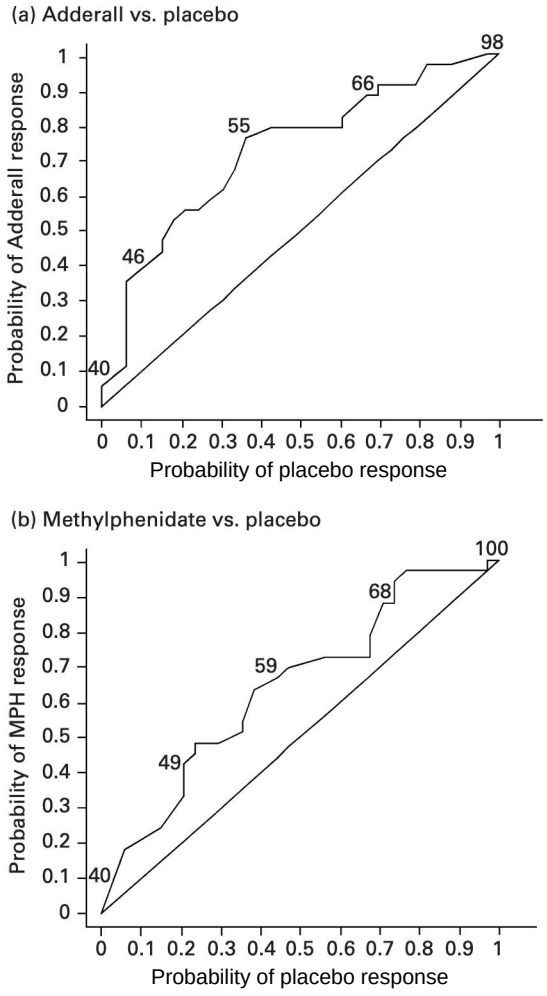

Figure 2. Abbreviated Symptoms Questionnaire — Teachers. Scores are t scores, which have a mean of 50 and standard deviation of 10. Scores of 65 or more are usually considered to be of clinical concern.

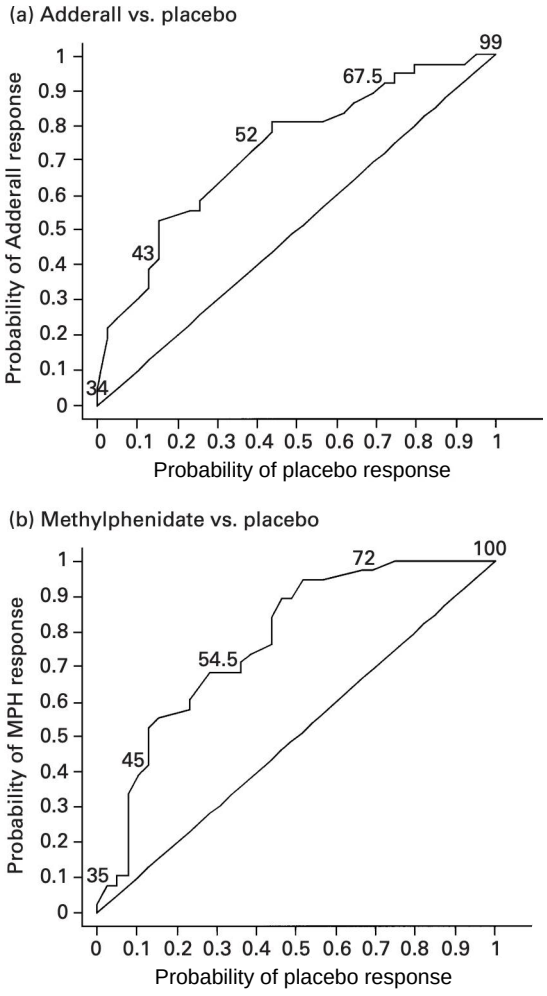

Figure 3. Abbreviated Symptoms Questionnaire — Parents. Scores are f scores, which have a mean of 50 and standard deviation of 10. Scores of 65 or more are usually considered to be of clinical concern.

drug—placebo response curves for each of the significant drug—placebo differences.

Teacher report data

Figures 1 and 2 show the results for the teacher report data. Figure l(a, b) shows the results for the School Situations Questionnaire (SSQ) for Adderall and MPH, respectively. Small values correspond to better outcome. For all possible definitions of' good response' (i.e. different SSQ cutting scores), each point on the curve shows the results of two calculations: the rate of response to drug and the rate of response to placebo. First consider the point labelled 0 in Figure la. This tells us the rates of drug and placebo response when we define a positive outcome as an SSQ score of 0 (no symptoms). For this point, we read from the horizontal axis that the rate of response is 11% for the placebo group; from the vertical axis we see that the response rate was 30% for the drug group. Sequential points further up the curve specify increasingly lenient thresholds for defining improvement. Thus, they show how the drug and placebo response rates change as we incrementally change the cutting score used to define improvement. For example, the next labelled point on the curve (labelled 0.6) represents the rates of response (to drug and placebo) when change is defined as an SSQ score of 0.6 or less. This point tells us that 40 % of the Adderall group, but only 18% of the placebo group, showed this degree of improvement.

On these curves, five points are labelled: the minimum, the 25th percentile, the median, the 75th percentile, and the maximum. For example, in Figure la we can see that

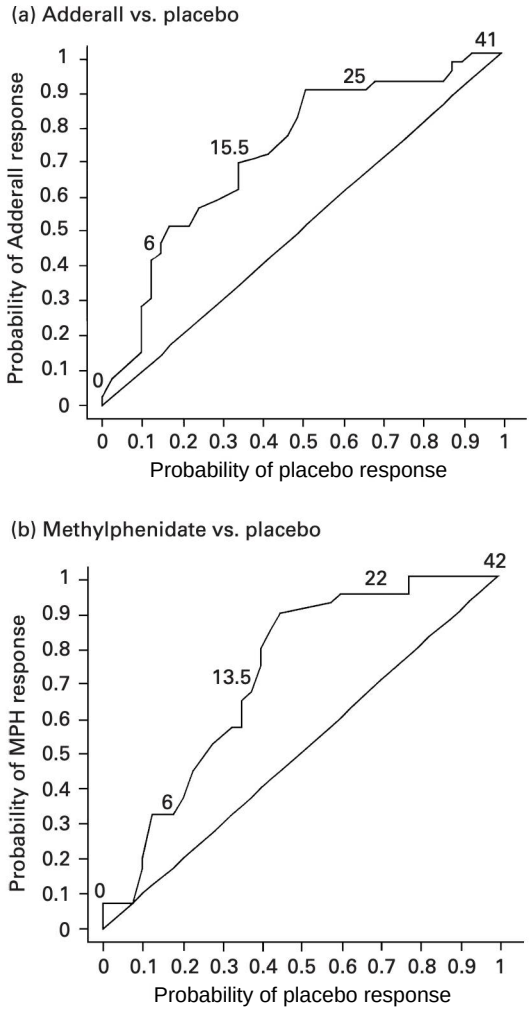

Figure 4. ADHD Rating Scale — Parents. Possible scores range from 0 (no symptoms) to 42 (severe symptoms).

the median score achieved was 3.2. The coordinates of this point (Adderall, 0.68; placebo, 0.41) tell us that 68% of Adderall patients achieved this level of improvement or better compared with 41 % of placebo patients. Knowing that the 25th percentile is 0.6 tells us that 25 % of subjects had a score of 0.6 or better and that 25 % scored between 0.6 and 3.2 (the median). Thus, the labelled points give us a rough idea of how the outcome scores are spread out among subjects.

The size of the drug effect is displayed by the degree to which the drug—placebo response curve rises above the line of no effect. If outcome on drug were worse than outcome on placebo, then the drug—placebo response curve would fall below the line of no effect. As Figure I shows, for both Adderall and MPH, the drug—placebo response curve is always above the diagonal Tine of no effect'. This shows that both drugs outperform placebo for all possible definitions of 'good response'.

A brief inspection of Figure I(a, b) shows that the curves from Adderall and MPH are very similar. Both rise above the diagonal line to the same degree and both have similar labels for the five labelled points. The AUC statistics for these two curves were 0.67 and 0.66. These show that Adderall and MPH outperform placebo 67 and 66% of the time, respectively.

Figure 2 shows results for teacher ratings on the ASQ. Because the Adderall curve (Figure 2a) is somewhat higher than the MPH curve (Figure 2b), the AUC for Adderall (0.72) is greater than that for MPH (0.64). But this difference was not statistically significant in the original report (Manos et al., 1999).

Parent report data

Figures 3 and 4 present results for parent report data. From Figure 3(a, b) we see that parent ratings on the ASQ show that both drugs are superior to placebo and that each has a similar effect. The AUCs for Adderall and MPH were 0.73 and 0.77, respectively. Comparing the parent ASQ ratings in Figure 3(a, b) with the teacher ASQ ratings in Figure 2(a, b) shows a very similar pattern of results for the parent and teacher ratings. Both sets of curves rise above the diagonal by about the same amount and both show a similar distribution of scores. The only slight difference is in the lower minimum scores for the parent ratings (Adderall, 34 vs. 40; MPH, 35 vs. 40). This suggests that parents are more likely to report lower symptom levels than teachers.

The parent ratings on the ADHD rating scale (Figure 4) are consistent with the other parent and teacher ratings in showing a similar pattern of results for Adderall and MPH. The AUCs were 0.72 for both Adderall and MPH.

Composite ratings

Figure 5 shows results for clinician composite ratings of the parent-reported data. This scale ranges from —5 (significant deterioration) to +5 (significant improvement). We again see that the curves are very similar for Adderall and MPH. The AUCs were 0.86 and 0.89, respectively. The curves in Figure 5 are especially interesting because they provide information about whether or not the drugs prevent worsening. A composite score of 0 indicates no change. In Figure 5a, by examining the graph axes corresponding to the point labelled 'O', we see that 100% of Adderall subjects had a score of 0 or better, i.e. no Adderall patients worsened. In contrast, only 89% of placebo subjects had a score of 0 or more.

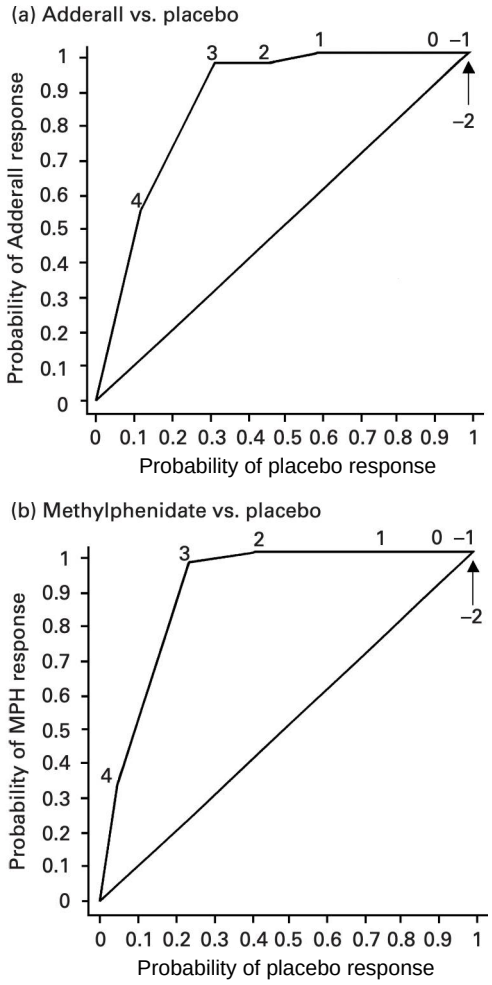

Figure 5. Composite rating. Based on parental report of weekly behaviour problems, the primary clinician rated the child's behaviour at the end of each week on a scale of — 5 (significant deterioration) to + 5 (significant improvement).

which indicates that 11% worsened. Likewise, in Figure 5b we see that no MPH patients worsened but 16% of placebo patients did. Thus, the response curves makes it clear that Adderall and MPH not only improve functioning, they also prevent worsening.

Discussion

We have extended the statistical results of Manos et al. (1999) by using drug—placebo response curves to describe the clinical significance of the efficacy of Adderall and MPH in the treatment of ADHD. Our presentation provides readers with a means of understanding the nature of drug effects and the degree to which they are clinically relevant. Instead of collapsing individual responses into means or single rates of response, the drug—placebo response curve shows the ability of each drug to improve outcome and limit worsening throughout the full range of outcome scores. These clinically relevant details are lost in a standard analysis.

Visual comparison of panels (a) and (b) in Figures 1—5 suggests that Adderall and MPH have equivalent efficacy, which is consistent with the finding of no statistical differences in the original report of Manos et al. (1999) on these data. Our analyses showed that both Adderall and MPH prevent worsening of symptoms. For example, in Figure 5, the 0 point on the composite rating scale is the point of no change. For both Adderall and MPH, the probability of 'no change or better' was 1.0. This means that no patients worsened on either drug. In contrast, for the placebo groups, the probability of 'no change or better' was about 0.85, meaning that 15% of patients worsen on placebo. From a clinical perspective, the worsening which occurs on placebo is important information which is not typically stressed or even mentioned in most published clinical trials. Knowledge of the risk of worsening without medication treatment is essential for clinicians to correctly communicate to patients and parents of patients the risks and benefits of stimulant therapy.

The value of drug—placebo response curve methods for rating scale data can be seen in Figures 2 and 3, which show ASQ results for teachers (Figure 2) and parents (Figure 3). These are presented as t scores, which have a mean of 50 and standard deviation of 10. Scores of 65 or more are usually considered to be of clinical concern. Because the drug—placebo response curve shows the entire distribution of scores, it provides useful facts about the distribution of response in drug and placebo groups. For example, in Figure 2a we see that from the point labelled 66, 90 % of Adderall-treated patients have scores less than 66 and are thus out of the clinically serious range. Only 68% of placebo subjects make an equal improvement. In addition to confirming the effect of Adderall at this clinical threshold, it also shows that 10% of Adderall-treated patients remain in the clinically serious range, which emphasizes the need for alternative treatments. Inspection of the MPH graphs lead to similar conclusions.

These two graphs also provide important information about the drugs' ability to lead to high levels of functioning. For example, patients with t scores of 50 or lower function as well as the best half of the general population. In Figure 3a we see that approx. 70% of Adderall-treated patients achieved this threshold compared with 35% of placebo-treated patients. Similar findings are seen for MPH. Both sets of graphs show that some placebo-treated patients do extremely well. Although we do not know if such placebo improvement would be long lasting, the finding of excellent placebo

response in a small subgroup should motivate research into the predictors of medication response.

As described by Faraone et al. (2000), the drug—placebo response curve might also generate psychometric hypotheses about drug—placebo differences. In this regard, the most notable difference among measures was the greater effect for the composite rating compared with the other ratings. Visually, we easily see this in the greater bowing-out of the curves in Figure 5 compared with the other figures. This difference leads to two psychometric hypotheses. Clinicians made the ratings based on a review of the standardized data, parental report and anecdotal data. Thus, one possibility is that the clinician rating may be more sensitive to drug effects because several sources of information were used and the information was evaluated by an expert. It is also possible that the composite rating may be more sensitive to improvements at the well end of the spectrum of functioning. This makes sense because the rating scales measure change within the range of pathology (i.e. reduction of symptoms) whereas the composite rating can be sensitive to non-symptomatic functional improvements.

This work must be considered in the context of its methodological limitations. Adderall and MPH were assigned by physician's choice. This non-random assignment may have affected the findings in unknown ways. Another limitation is the use of a clinic-based sample that caters for primarily middle-class families. That will limit the generalizability of our findings. Also, the use of a fixed dose design may not optimally model the clinical administration of these medications. We must also consider several threats to the internal validity of the study, which may have compromised our results. These include regression towards the mean, test sensitization, and demand characteristics. Because of these threats, we must be cautious in the interpretation of our results. Despite these limitations, our results clarify the clinical significance of each medication's efficacy when compared with placebo. Both drugs prevent worsening and, for a majority of patients, lead to improvements that are well into the normal range.

Acknowledgement

This study was in part supported by funding from Shire Pharmaceutical Development Inc. to Dr Faraone.

References

Barkley RA (1990). Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment. New York: Guilford Press.

Biederman J, Spencer T, Wilens T (1997). Psychopharmacology in children and adolescents. In: Wiener J (Ed.), Textbook of Child and Adolescent Psychiatry (2nd edn) (pp. 779—813). Washington, DC: American Psychiatric Press.

Colditz GA, Miller JN, Mosteller F (1988). Measuring gain in the evaluation of medical technology. The probability of a better outcome. International Journal of Technological Assessment of Health Care 4, 637—642.

Conners CK (1969). A teacher rating scale for use in drug studies with children. American Journal of Psychiatry 126, 884-888.

DuPaul G (1991). Parent and teacher ratings of ADHD symptoms: psychometric properties in a community-based sample. Journal of Clinical Child Psychology 20, 245—253.

Faraone SV, Biederman J, Spencer TJ, Wilens TE (2000). The drug—placebo response curve: a new method for assessing drug effects in clinical trials. Journal of Clinical Psychopharmacology 20, 673—679.

Faraone SV, Pliszka SR, Olvera RL, Skolnik R, Biederman J (2001). Efficacy of adderall and methylphenidate in attention-deficit/hyperactivity disorder: a drug—placebo and drug—drug response curve analysis. Journal of Child and Adolescent Psychopharmacology 11, 171—180.

Hanley JA, McNeil BJ (1982). The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143, 29—36.

Manos MJ, Short EJ, Findling RL (1999). Differential effectiveness of methylphenidate and Adderall in school-age youths with attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 38, 813—819.

McNeil BJ, Hanley JA (1984). Statistical approaches to the analysis of receiver operating characteristic (ROC) curves. Medical Decision Making 4, 137—150.

Pelham WE, Aronoff HR, Midlam JK, Shapiro CJ, Gnagy EM, Chronis AM, Onyango AN, Forehand G, Nguyen A, Waxmonsky J (1999a). A comparison of ritalin and adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. Pediatrics 103, e43.

Pelham WE, Gnagy EM, Chronis AM, Burrows-MacLean L, Fabiano GA, Onyango AN, Meichenbaum DL, Williams A, Aronoff HR, Steiner RL (1999b). A comparison of morning-only and moming/late afternoon Adderall to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder. Pediatrics 104, 1300-1311.

Pliszka SR, Browne RG, Olvera RL, Wynne SK (2000). A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 39, 619—626.

Rapport MD, DuPaul GJ, Kelly KL (1989a). Attention deficit hyperactivity disorder and methylphenidate: the relationship between gross body weight and drug response in children. Psychopharmacology Bulletin 25, 285—290.

Rapport MD, Quinn SO, DuPaul GJ, Quinn EP, Kelly KL

(1989b). Attention deficit disorder with hyperactivity and methylphenidate: the effects of dose and mastery level on children's learning performance. Journal of Abnormal Child Psychology 17, 669—689.

Siegel B, Vukicevic J, Elliott GR, Kraemer HC (1989). The use of signal detection theory to assess DSM-III-R criteria for autistic disorder. Journal of the American Academy of Child and Adolescent Psychiatry 28, 542—548.

Siegel B, Vukicevic J, Spitzer RL (1990). Using signal detection methodology to revise DSM-III-R: re-analysis of the DSM-III-R national field trials for autistic disorder. Journal of Psychiatric Research 24, 293—311.

Swanson J, Wigal S, Greenhill L, Browne R, Waslik B, Lerner M, Williams L, Flynn D, Agler D, Crowley K, Fineberg E, Baren M, Cantwell D (1998). Analog classroom assessment of adderall in children with ADHD. Journal of the American Academy of Child and Adolescent Psychiatry 37, 519—526.

Swets JA, Pickett RM (1982). Evaluation of Diagnostic Systems: Methods From Signal Detection Theory. New York: Academic Press.