Drug Class Review

Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

Final Update 5 Report

Appendixes and Evidence Tables

July 2015

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Shading indicates new information for Update 5.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

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Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

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in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

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Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intent to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intent to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (heart attack).

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Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta-analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

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effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intent-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

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Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

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Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

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Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a crossover trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

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Appendix B. Search strategies for Update 5

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to March Week 5 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <April 01, 2015>
Search Strategy:
---
1 mixed amphetamine salts.mp. (94)
2 adderall XR.mp. (43)
3 atomoxetine hydrochloride.mp. (62)
4 atomoxetine.mp. (1224)
5 strattera.mp. (53)
6 clonidine hydrochloride.mp. (210)
7 clonidine.mp. (16854)
8 catapres.mp. (90)
9 catapres TTS.mp. (18)
10 kapvay.mp. (0)
11 dexmethylphenidate hydrochloride.mp. (15)
12 dexmethylphenidate.mp. (71)
13 focalin.mp. (19)
14 focalin XR.mp. (6)
15 dextroamphetamine sulfate.mp. (92)
16 dextroamphetamine.mp. (6761)
17 exp Dextroamphetamine/ (6581)
18 dexedrine.mp. (80)
19 dexedrine spansule.mp. (2)
20 guanfacine hydrochloride.mp. (11)
21 guanfacine.mp. (845)
22 intuniv.mp. (11)
23 tenex.mp. (6)
24 lisdexamfetamine dimesylate.mp. (166)
25 lisdexamfetamine.mp. (200)
26 vyvanse.mp. (29)
27 methamphetamine hydrochloride.mp. (70)
28 methamphetamine.mp. (9745)
29 exp Methamphetamine/ (7483)
30 desoxyn.mp. (8)
31 methylphenidate.mp. (7255)
32 exp Methylphenidate/ (5860)
33 daytrana.mp. (9)
34 methylphenidate hydrochloride.mp. (183)
35 biphentin.mp. (2)
36 concerta.mp. (105)
37 metadate CD.mp. (20)
38 metadate ER.mp. (0)
39 methylin.mp. (3)
40 methylin ER.mp. (0)

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41 quillivant XR.mp. (1)
42 ritalin.mp. (621)
43 ritalin LA.mp. (22)
44 ritalin-SR.mp. (5)
45 modafinil.mp. (1327)
46 alertec.mp. (0)
47 provigil.mp. (37)
48 armodafinil.mp. (119)
49 nuvigil.mp. (5)
50 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (41990)
51 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (20960)
52 Attention deficit disorder.mp. (21398)
53 attention deficit$.mp. (28240)
54 adhd.mp. (15366)
55 51 or 52 or 53 or 54 (29184)
56 50 and 55 (5147)
57 (201105$ or 201106$ or 201107$ or 201108$ or 201109$ or 20111$ or 2012$ or 2013$ or 2014$ or 2015$).ed. (3739341)
58 56 and 57 (1336)
59 limit 58 to (english language and humans) (921)
60 limit 59 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial or "review") (510)
61 observational stud$.mp. or exp Cohort Studies/ or cohort$.mp. or exp Retrospective Studies/ or retrospective$.mp. (1669433)
62 59 and 61 (172)
63 60 or 62 (604)

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Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to March Week 5 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <April 01, 2015>
Search Strategy:
---
1 mixed amphetamine salts.mp. (94)
2 adderall XR.mp. (43)
3 atomoxetine hydrochloride.mp. (62)
4 atomoxetine.mp. (1224)
5 strattera.mp. (53)
6 clonidine hydrochloride.mp. (210)
7 clonidine.mp. (16854)
8 catapres.mp. (90)
9 catapres TTS.mp. (18)

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10 kapvay.mp. (0)
11 dexmethylphenidate hydrochloride.mp. (15)
12 dexmethylphenidate.mp. (71)
13 focalin.mp. (19)
14 focalin XR.mp. (6)
15 dextroamphetamine sulfate.mp. (92)
16 dextroamphetamine.mp. (6761)
17 exp Dextroamphetamine/ (6581)
18 dexedrine.mp. (80)
19 dexedrine spansule.mp. (2)
20 guanfacine hydrochloride.mp. (11)
21 guanfacine.mp. (845)
22 intuniv.mp. (11)
23 tenex.mp. (6)
24 lisdexamfetamine dimesylate.mp. (166)
25 lisdexamfetamine.mp. (200)
26 vyvanse.mp. (29)
27 methamphetamine hydrochloride.mp. (70)
28 methamphetamine.mp. (9745)
29 exp Methamphetamine/ (7483)
30 desoxyn.mp. (8)
31 methylphenidate.mp. (7255)
32 exp Methylphenidate/ (5860)
33 daytrana.mp. (9)
34 methylphenidate hydrochloride.mp. (183)
35 biphentin.mp. (2)
36 concerta.mp. (105)
37 metadate CD.mp. (20)
38 metadate ER.mp. (0)
39 methylin.mp. (3)
40 methylin ER.mp. (0)
41 quillivant XR.mp. (1)
42 ritalin.mp. (621)
43 ritalin LA.mp. (22)
44 ritalin-SR.mp. (5)
45 modafinil.mp. (1327)
46 alertec.mp. (0)
47 provigil.mp. (37)
48 armodafinil.mp. (119)
49 nuvigil.mp. (5)
50 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (41990)
51 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (20960)
52 Attention deficit disorder.mp. (21398)

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53 attention deficit$.mp. (28240)
54 adhd.mp. (15366)
55 51 or 52 or 53 or 54 (29184)
56 50 and 55 (5147)
57 diversion.mp. (18587)
58 exp Substance-Related Disorders/ (228858)
59 ((drug$ or substance$ or stimula$) adj3 (abus$ or addict$)).mp. (73622)
60 (misuse$ or misusing).mp. (16372)
61 exp Behavior, Addictive/ (5556)
62 (addict$ adj3 behav$).mp. (7760)
63 (drug$ adj3 seek$).mp. (2774)
64 57 or 58 or 59 or 60 or 61 or 62 or 63 (286521)
65 56 and 64 (519)
66 illegal$.mp. (8597)
67 unlawful$.mp. (430)
68 illicit$.mp. (10979)
69 criminal$.mp. (22752)
70 66 or 67 or 68 or 69 (40980)
71 56 and 70 (41)
72 65 or 71 (530)
73 limit 72 to (english language and humans) (386)
74 (201105$ or 201106$ or 201107$ or 201108$ or 201109$ or 20111$ or 2012$ or 2013$ or 2014$ or 2015$).ed. (3739341)
75 73 and 74 (96)
76 limit 75 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial or "review") (58)
77 observational stud$.mp. or exp Cohort Studies/ or cohort$.mp. or exp Retrospective Studies/ or retrospective$.mp. (1669433)
78 75 and 77 (14)
79 76 or 78 (64)

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Database: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2015>
Search Strategy:
---
1 mixed amphetamine salts.mp. (46)
2 adderall XR.mp. (19)
3 atomoxetine hydrochloride.mp. (13)
4 atomoxetine.mp. (258)
5 strattera.mp. (7)
6 clonidine hydrochloride.mp. (66)
7 clonidine.mp. (2686)
8 catapres.mp. (19)
9 catapres TTS.mp. (7)

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10 kapvay.mp. (0)
11 dexmethylphenidate hydrochloride.mp. (8)
12 dexmethylphenidate.mp. (34)
13 focalin.mp. (9)
14 focalin XR.mp. (3)
15 dextroamphetamine sulfate.mp. (28)
16 dextroamphetamine.mp. (589)
17 exp Dextroamphetamine/ (510)
18 dexedrine.mp. (15)
19 dexedrine spansule.mp. (1)
20 guanfacine hydrochloride.mp. (5)
21 guanfacine.mp. (148)
22 intuniv.mp. (3)
23 tenex.mp. (0)
24 lisdexamfetamine dimesylate.mp. (94)
25 lisdexamfetamine.mp. (112)
26 vyvanse.mp. (2)
27 methamphetamine hydrochloride.mp. (1)
28 methamphetamine.mp. (398)
29 exp Methamphetamine/ (205)
30 desoxyn.mp. (0)
31 methylphenidate.mp. (1572)
32 exp Methylphenidate/ (1011)
33 daytrana.mp. (0)
34 methylphenidate hydrochloride.mp. (67)
35 biphentin.mp. (1)
36 concerta.mp. (43)
37 metadate CD.mp. (9)
38 metadate ER.mp. (0)
39 methylin.mp. (0)
40 methylin ER.mp. (0)
41 quillivant XR.mp. (0)
42 ritalin.mp. (113)
43 ritalin LA.mp. (11)
44 ritalin-SR.mp. (2)
45 modafinil.mp. (385)
46 alertec.mp. (0)
47 provigil.mp. (9)
48 armodafinil.mp. (67)
49 nuvigil.mp. (2)
50 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (5870)
51 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (1498)
52 Attention deficit disorder.mp. (1927)

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53 attention deficit$.mp. (2332)
54 adhd.mp. (1646)
55 51 or 52 or 53 or 54 (2517)
56 50 and 55 (1370)
57 limit 56 to english language (1159)
58 limit 57 to yr="2011 -Current" (328)

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Database: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2015>
Search Strategy:
---
1 mixed amphetamine salts.mp. (46)
2 adderall XR.mp. (19)
3 atomoxetine hydrochloride.mp. (13)
4 atomoxetine.mp. (258)
5 strattera.mp. (7)
6 clonidine hydrochloride.mp. (66)
7 clonidine.mp. (2686)
8 catapres.mp. (19)
9 catapres TTS.mp. (7)
10 kapvay.mp. (0)
11 dexmethylphenidate hydrochloride.mp. (8)
12 dexmethylphenidate.mp. (34)
13 focalin.mp. (9)
14 focalin XR.mp. (3)
15 dextroamphetamine sulfate.mp. (28)
16 dextroamphetamine.mp. (589)
17 exp Dextroamphetamine/ (510)
18 dexedrine.mp. (15)
19 dexedrine spansule.mp. (1)
20 guanfacine hydrochloride.mp. (5)
21 guanfacine.mp. (148)
22 intuniv.mp. (3)
23 tenex.mp. (0)
24 lisdexamfetamine dimesylate.mp. (94)
25 lisdexamfetamine.mp. (112)
26 vyvanse.mp. (2)
27 methamphetamine hydrochloride.mp. (1)
28 methamphetamine.mp. (398)
29 exp Methamphetamine/ (205)
30 desoxyn.mp. (0)
31 methylphenidate.mp. (1572)
32 exp Methylphenidate/ (1011)
33 daytrana.mp. (0)
34 methylphenidate hydrochloride.mp. (67)

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35 biphentin.mp. (1)
36 concerta.mp. (43)
37 metadate CD.mp. (9)
38 metadate ER.mp. (0)
39 methylin.mp. (0)
40 methylin ER.mp. (0)
41 quillivant XR.mp. (0)
42 ritalin.mp. (113)
43 ritalin LA.mp. (11)
44 ritalin-SR.mp. (2)
45 modafinil.mp. (385)
46 alertec.mp. (0)
47 provigil.mp. (9)
48 armodafinil.mp. (67)
49 nuvigil.mp. (2)
50 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (5870)
51 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (1498)
52 Attention deficit disorder.mp. (1927)
53 attention deficit$.mp. (2332)
54 adhd.mp. (1646)
55 51 or 52 or 53 or 54 (2517)
56 50 and 55 (1370)
57 diversion.mp. (304)
58 substance abuse.mp. or exp Substance-Related Disorders/ (9555)
59 misuse.mp. (470)
60 addictive behavior.mp. or exp Behavior, Addictive/ (336)
61 57 or 58 or 59 or 60 (10254)
62 56 and 61 (59)
63 limit 62 to english language (57)
64 limit 63 to yr="2011 -Current" (24)

****

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 2015>
Search Strategy:
---
1 mixed amphetamine salts.mp. (4)
2 adderall XR.mp. (0)
3 atomoxetine hydrochloride.mp. (0)
4 atomoxetine.mp. (33)
5 strattera.mp. (4)
6 clonidine hydrochloride.mp. (1)
7 clonidine.mp. (114)

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8 catapres.mp. (7)
9 catapres TTS.mp. (0)
10 kapvay.mp. (1)
11 dexmethylphenidate hydrochloride.mp. (0)
12 dexmethylphenidate.mp. (6)
13 focalin.mp. (7)
14 focalin XR.mp. (0)
15 dextroamphetamine sulfate.mp. (2)
16 dextroamphetamine.mp. (24)
17 [exp Dextroamphetamine/] (0)
18 dexedrine.mp. (7)
19 dexedrine spansule.mp. (0)
20 guanfacine hydrochloride.mp. (0)
21 guanfacine.mp. (18)
22 intuniv.mp. (0)
23 tenex.mp. (0)
24 lisdexamfetamine dimesylate.mp. (0)
25 lisdexamfetamine.mp. (3)
26 vyvanse.mp. (2)
27 methamphetamine hydrochloride.mp. (0)
28 methamphetamine.mp. (30)
29 [exp Methamphetamine/] (0)
30 desoxyn.mp. (1)
31 methylphenidate.mp. (61)
32 [exp Methylphenidate/] (0)
33 daytrana.mp. (2)
34 methylphenidate hydrochloride.mp. (4)
35 biphentin.mp. (1)
36 concerta.mp. (9)
37 metadate CD.mp. (0)
38 metadate ER.mp. (0)
39 methylin.mp. (2)
40 methylin ER.mp. (0)
41 quillivant XR.mp. (0)
42 ritalin.mp. (14)
43 ritalin LA.mp. (1)
44 ritalin-SR.mp. (0)
45 modafinil.mp. (34)
46 alertec.mp. (0)
47 provigil.mp. (3)
48 armodafinil.mp. (3)
49 nuvigil.mp. (1)
50 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (217)

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51 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (23)
52 Attention deficit disorder.mp. (33)
53 attention deficit$.mp. (109)
54 adhd.mp. (67)
55 51 or 52 or 53 or 54 (113)
56 50 and 55 (44)
57 limit 56 to yr="2011 -Current" (28)

****

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 2015>
Search Strategy:
---
1 mixed amphetamine salts.mp. (4)
2 adderall XR.mp. (0)
3 atomoxetine hydrochloride.mp. (0)
4 atomoxetine.mp. (33)
5 strattera.mp. (4)
6 clonidine hydrochloride.mp. (1)
7 clonidine.mp. (114)
8 catapres.mp. (7)
9 catapres TTS.mp. (0)
10 kapvay.mp. (1)
11 dexmethylphenidate hydrochloride.mp. (0)
12 dexmethylphenidate.mp. (6)
13 focalin.mp. (7)
14 focalin XR.mp. (0)
15 dextroamphetamine sulfate.mp. (2)
16 dextroamphetamine.mp. (24)
17 [exp Dextroamphetamine/] (0)
18 dexedrine.mp. (7)
19 dexedrine spansule.mp. (0)
20 guanfacine hydrochloride.mp. (0)
21 guanfacine.mp. (18)
22 intuniv.mp. (0)
23 tenex.mp. (0)
24 lisdexamfetamine dimesylate.mp. (0)
25 lisdexamfetamine.mp. (3)
26 vyvanse.mp. (2)
27 methamphetamine hydrochloride.mp. (0)
28 methamphetamine.mp. (30)
29 [exp Methamphetamine/] (0)
30 desoxyn.mp. (1)
31 methylphenidate.mp. (61)
32 [exp Methylphenidate/] (0)

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33 daytrana.mp. (2)
34 methylphenidate hydrochloride.mp. (4)
35 biphentin.mp. (1)
36 concerta.mp. (9)
37 metadate CD.mp. (0)
38 metadate ER.mp. (0)
39 methylin.mp. (2)
40 methylin ER.mp. (0)
41 quillivant XR.mp. (0)
42 ritalin.mp. (14)
43 ritalin LA.mp. (1)
44 ritalin-SR.mp. (0)
45 modafinil.mp. (34)
46 alertec.mp. (0)
47 provigil.mp. (3)
48 armodafinil.mp. (3)
49 nuvigil.mp. (1)
50 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (217)
51 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (23)
52 Attention deficit disorder.mp. (33)
53 attention deficit$.mp. (109)
54 adhd.mp. (67)
55 51 or 52 or 53 or 54 (113)
56 50 and 55 (44)
57 diversion.mp. (69)
58 substance abuse.mp. (269)
59 misuse.mp. (257)
60 addictive behavior.mp. (4)
61 57 or 58 or 59 or 60 (494)
62 56 and 61 (18)
63 limit 62 to yr="2011-Current" (13)

****

Database: PsycINFO <1806 to March Week 5 2015>
Search Strategy:
---
1 mixed amphetamine salts.mp. (68)
2 adderall XR.mp. (27)
3 atomoxetine hydrochloride.mp. (21)
4 atomoxetine.mp. (691)
5 strattera.mp. (31)
6 clonidine hydrochloride.mp. (30)

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7 clonidine.mp. (2152)
8 catapres.mp. (11)
9 catapres TTS.mp. (0)
10 kapvay.mp. (0)
11 dexmethylphenidate hydrochloride.mp. (6)
12 dexmethylphenidate.mp. (33)
13 focalin.mp. (15)
14 focalin XR.mp. (5)
15 dextroamphetamine sulfate.mp. (187)
16 dextroamphetamine.mp. (2446)
17 exp Dextroamphetamine/ (1974)
18 dexedrine.mp. (82)
19 dexedrine spansule.mp. (0)
20 guanfacine hydrochloride.mp. (2)
21 guanfacine.mp. (239)
22 intuniv.mp. (4)
23 tenex.mp. (2)
24 lisdexamfetamine dimesylate.mp. (86)
25 lisdexamfetamine.mp. (116)
26 vyvanse.mp. (18)
27 methamphetamine hydrochloride.mp. (22)
28 methamphetamine.mp. (4109)
29 exp Methamphetamine/ (2979)
30 desoxyn.mp. (5)
31 methylphenidate.mp. (4165)
32 exp Methylphenidate/ (3041)
33 daytrana.mp. (6)
34 methylphenidate hydrochloride.mp. (104)
35 biphentin.mp. (2)
36 concerta.mp. (78)
37 metadate CD.mp. (9)
38 metadate ER.mp. (0)
39 methylin.mp. (2)
40 methylin ER.mp. (0)
41 quillivant XR.mp. (0)
42 ritalin.mp. (512)
43 ritalin LA.mp. (5)
44 ritalin-SR.mp. (1)
45 modafinil.mp. (690)
46 alertec.mp. (0)
47 provigil.mp. (21)
48 armodafinil.mp. (47)
49 nuvigil.mp. (1)
50 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (13710)

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51 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (15432)
52 Attention deficit disorder.mp. (20618)
53 attention deficit$.mp. (26385)
54 adhd.mp. (20034)
55 51 or 52 or 53 or 54 (28073)
56 50 and 55 (3375)
57 limit 56 to yr="2011- Current" (941)
58 limit 57 to (human and english language) (745)

****

Database: PsycINFO <1806 to March Week 5 2015>
Search Strategy:
---
1 mixed amphetamine salts.mp. (68)
2 adderall XR.mp. (27)
3 atomoxetine hydrochloride.mp. (21)
4 atomoxetine.mp. (691)
5 strattera.mp. (31)
6 clonidine hydrochloride.mp. (30)
7 clonidine.mp. (2152)
8 catapres.mp. (11)
9 catapres TTS.mp. (0)
10 kapvay.mp. (0)
11 dexmethylphenidate hydrochloride.mp. (6)
12 dexmethylphenidate.mp. (33)
13 focalin.mp. (15)
14 focalin XR.mp. (5)
15 dextroamphetamine sulfate.mp. (187)
16 dextroamphetamine.mp. (2446)
17 exp Dextroamphetamine/ (1974)
18 dexedrine.mp. (82)
19 dexedrine spansule.mp. (0)
20 guanfacine hydrochloride.mp. (2)
21 guanfacine.mp. (239)
22 intuniv.mp. (4)
23 tenex.mp. (2)
24 lisdexamfetamine dimesylate.mp. (86)
25 lisdexamfetamine.mp. (116)
26 vyvanse.mp. (18)
27 methamphetamine hydrochloride.mp. (22)
28 methamphetamine.mp. (4109)
29 exp Methamphetamine/ (2979)
30 desoxyn.mp. (5)
31 methylphenidate.mp. (4165)

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32 exp Methylphenidate/ (3041)
33 daytrana.mp. (6)
34 methylphenidate hydrochloride.mp. (104)
35 biphentin.mp. (2)
36 concerta.mp. (78)
37 metadate CD.mp. (9)
38 metadate ER.mp. (0)
39 methylin.mp. (2)
40 methylin ER.mp. (0)
41 quillivant XR.mp. (0)
42 ritalin.mp. (512)
43 ritalin LA.mp. (5)
44 ritalin-SR.mp. (1)
45 modafinil.mp. (690)
46 alertec.mp. (0)
47 provigil.mp. (21)
48 armodafinil.mp. (47)
49 nuvigil.mp. (1)
50 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (13710)
51 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (15432)
52 Attention deficit disorder.mp. (20618)
53 attention deficit$.mp. (26385)
54 adhd.mp. (20034)
55 51 or 52 or 53 or 54 (28073)
56 50 and 55 (3375)
57 diversion.mp. (2075)
58 substance abuse.mp. or exp Substance-Related Disorders/ (29055)
59 misuse.mp. (8136)
60 addictive behavior.mp. or exp Behavior, Addictive/ (1115)
61 57 or 58 or 59 or 60 (39232)
62 56 and 61 (128)
63 limit 62 to (human and english language) (104)
64 limit 63 to yr="2011 -Current" (34)

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Appendix C. Excluded studies for Update 5

The following full-text publications were considered for inclusion but failed to meet the criteria for this report. See previous versions of the report on the Drug Effectiveness Review Project website for studies excluded previously.

Exclusion codes: 1=non-English language, 2=ineligible outcome, 3=ineligible intervention, 4=ineligible population, 5=ineligible publication type, 6=ineligible study design, 7=study not obtainable, 8=outdated or ineligible systematic review

Excluded Studies	Exclusion Code
1. Adler LA, Dirks B, Deas P, et al. Self-Reported quality of life in adults with attention-deficit/hyperactivity disorder and executive function impairment treated with lisdexamfetamine dimesylate: a randomized, double-blind, multicenter, placebo-controlled, parallel-group study. *BMC Psychiatry*. 2013;13:253.	6
2. Adler LA, Dirks B, Deas PF, et al. Lisdexamfetamine dimesylate in adults with attention-deficit/ hyperactivity disorder who report clinically significant impairment in executive function: results from a randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry.* Jul 2013;74(7):694-702.	6
3. Agarwal R, Goldenberg M, Perry R, IsHak WW. The quality of life of adults with attention deficit hyperactivity disorder: A systematic review. *Innovations in Clinical Neuroscience.* May-Jun 2012;9(5-6):10-21.	8
4. Arcieri R, Germinario EA, Bonati M, et al. Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. *Journal of Child & Adolescent Psychopharmacology.* Dec 2012;22(6):423-431.	2
5. Arnold VK, Feifel D, Earl CQ, Yang R, Adler LA. A 9-week, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study to evaluate the efficacy and safety of modafinil as treatment for adults with ADHD. *Journal of Attention Disorders*. Feb 2014;18(2):133-144.	6
6. Ayaz M, Ayaz AB, Soylu N, Yuksel S. Medication persistence in Turkish children and adolescents with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology.* Oct 2014;24(8):442-447.	2
7. Banaschewski T, Soutullo C, Lecendreux M, et al. The child health and illness profile as a measure of health-related quality of life in stimulant-treated children and adolescents with ADHD. *European child & adolescent psychiatry.* START: 2013 Jul 6 CONFERENCE END: 2013 Jul 10, 15th International Congress of European Society for Child and Adolescent Psychiatry, ESCAP 2013 Dublin Ireland;22(2 SUPPL. 1):S125-S126.	5
8. Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Leibson CL, Jacobsen SJ. Long-term stimulant medication treatment of attention-deficit/hyperactivity disorder: Results from a population-based study. *Journal of Developmental and Behavioral Pediatrics.* Sep 2014;35(7):448-457.	5
9. Barner JC, Khoza S, Oladapo A. ADHD medication use, adherence, persistence and cost among Texas Medicaid children. *Current Medical Research & Opinion.* 2011;27 Suppl 2:13-22.	2
10. Bastiaens L. Improvement in global psychopathology increases quality of life during treatment of ADHD with atomoxetine or stimulants. *Psychiatric Quarterly.* Dec 2011;82(4):303-308.	6

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Excluded Studies	Exclusion Code
11. Biederman J, Fried R, Hammerness P, et al. The effects of lisdexamfetamine dimesylate on driving behaviors in young adults with ADHD assessed with the Manchester driving behavior questionnaire. *Journal of Adolescent Health.* Dec 2012;51(6):601-607.	6
12. Biederman J, Mick E, Spencer T, Surman C, Faraone SV. Is response to OROS-methylphenidate treatment moderated by treatment with antidepressants or psychiatric comorbidity? A secondary analysis from a large randomized double blind study of adults with ADHD. *CNS Neurosci Ther.* Feb 2012;18(2):126-132.	6
13. Brams M, Giblin J, Gasior M, Gao J, Wigal T. Effects of open-label lisdexamfetamine dimesylate on self-reported quality of life in adults with ADHD. *Postgrad Med.* May 2011;123(3):99-108.	6
14. Buitelaar JK, Kooij JJS, Ramos-Quiroga JA, et al. Predictors of treatment outcome in adults with ADHD treated with OROS methylphenidate. *Progress in Neuro-Psychopharmacology & Biological Psychiatry.* Mar 30 2011;35(2):554-560.	6
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Appendix D. Abbreviations used in appendixes and evidence tables

Abbreviation	Term
(ER) d-MPH	long-acting extended-release dexmethylphenidate
A'	(calculated as 0.5+[(h−f)+(h−f)2]/[4*h*(1−f)]): a signal detection measure of sensitivity to the target, regardless of response tendency.
ACDS	Adult ADHD Clinician Diagnostic Scale
ADHD	attention-deficit/hyperactivity disorder
ADHD-C	ADHD-Combined type
ADHD-H	ADHD-Hyperactive-impulsive type
ADHD-I	ADHD-Inattentive type
ADHD-RS	Attention-Deficit/Hyperactivity Disorder Rating Scale
ADHD-RS-IV	ADHD Rating Scale version IV
AE(s)	Adverse Event(s)
AIFA	Italian Medicine Agency
AMPH	amphetamine
ATX	atomoxetine
AUC	Area under the score vs. time curve
bid	2 times daily
CBCL	Child Behavior Checklist
CGI-I / CGI-S	Clinical Global Impressions-Improvement (CGI-I) / Clinical Global Impression-Severity score
CPT	Conners' Continuous Performance Test
d	day(s)
D,L-MPH-ER	Racemic methylphenidate hydrochloride
DSM-II	Diagnostic and Statistical Manual of Mental Disorders, 2nd edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
ER MAS	ER mixed amphetamine salts
GXR	Guanfacine extended-release
IQ	Intelligence quotient
IR	Immediate Release
LDX	Lisdexamfetamine dimesylate
LS	Least-squares mean change
mg/kg	milligram/kilogram
MPH	OROS (osmotic release oral system)-methylphenidate
NIMH	National Institute of Mental Health
NR	Not Reported
ODD	oppositional defiant disorder
qid	once daily
RCI	Reliable Change Index
RT	reaction time
SD	Standard Deviation

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Abbreviation	Term
SKAMP	Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale
TASS	Time-Sensitive ADHD Symptom Scale
TEAE(s)	treatment-emergent adverse events
tid	3 times daily
US	United States
vs	Versus
WFIRS(-P)	Weiss Functional Impairment Rating Scale (-Parent Report)
XR	extended release
y	year(s)

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Adler 2011 US NCT00468143 (Fair)	Men or women aged 18 to 55 y who met DSM-IV-TR criteria for ADHD, as assessed by the Adult ADHD Clinician Diagnostic Scale (ACDS) version 1.2.	A. Mixed amphetamine salts immediate release (MAS IR) tid 15, 30, or 45 mg B. Mixed amphetamine salts extended release (MAS XR) QD 15, 30 or 45 mg. At visits 3, 4, 7 and 8 dose increased. At discretion of investigator, doses could be lowered at visits 4 and 8. Duration of study: 9 weeks	NR	Age (mean), y: 35.7 Gender, % female: 45.2 Ethnicity, %: Caucasian: 77.4 African American: 11.3 Hispanic: 8.1 Asian: 6.5 American Indian or Alaskan: 1.2 Other/mixed ethnicity: 4.8	NR	62	13/NR/49
Amiri 2008 Iran (Fair)	Patients were 6-15 years old who met the DSM-IV-TR diagnostic criteria for ADHD. They had total and/or subscale scores on ADHD-RS-IV, school version at least 1.5 SD above norms for patient's age and gender. Patients were excluded if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders; any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk and mental retardation; they had a clinically significant chronic medical condition, including organic brain disorder, seizures and current abuse or dependence on drugs within 6 months; hypertension, hypotension and habitual consumption of more than 250mg/day of caffeine.	Modafinil Dependent on weight: 200mg/day for <30 kg and 300mg/day for >30 kg Methylphenidate Dependent on weight: 20mg/day for <30 kg and 30mg/day for >30 kg	NR	Mean age: 9.2 years (Modafinil) vs 8.96 years (Methylphenidate) 78.3% male 100% Persian	NR	60	5 withdrew: 2 from modafinil group vs 3 from methylphenidate group Lost to FU=NR Analyzed=60

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Adler 2011 US NCT00468143 (Fair)	MAS IR vs MAS XR Change in mean scores (SD) from baseline to week 3: ADHD-RS in-clinic: -10.5 (9.3) vs-13.8 (9.2), z= -8.4, p-value <0.001 ADHD-RS evening: -8.3 (9.8) vs -9.6 (10.0), z= -4.86, p-value <0.001 TASS in-clinic: -7.4 (10.4) vs -9.7 (11.8), z= -4.57, p-value <0.001 TASS evening: -10.1 (9.3) vs -11.3 (9.2), z= -4.99, p-value <0.001 CGI-S: -1.0 (0.8) vs -1.2 (1.0), z=3.77, p= 0.003	Treatment-emergent AEs, % total: Withdrawal due to AE: 9.7 Insomnia: 43.5 loss of appetite/anorexia: 40.3 Anxiety: 11.3 Abuse potential, tics, and sexual dysfunction: NR	Total withdrawals, no.: 13 Withdrawal due to AE, %: 9.7	Shire Development, INC.	
Amiri 2008 Iran (Fair)	Modafinil vs Methylphenidate Change in Parent ADHD-RS-IV from baseline at day 42: -24.36 vs -22.66 % of responders based on Parent ADHD-RS-IV: 73.33% vs 70% Change in Teacher ADHD-RS-IV from baseline at day 42: -20.53 vs -21.33 % of responders based on Teacher ADHD-RS-IV: 73.33% vs 73.33%	Modafinil vs Methylphenidate Abdominal pain: 4 vs 7 Anxiety, nervousness: 3 vs 4 Decreased appetite: 18 vs 26 (p=0.03) Sadness: 4 vs 6 Difficulty falling asleep: 2 vs 8 (p=0.05) Weight loss: 3 vs 7 Nausea: 2 vs 4 Dry mouth: 7 vs 10 Irritability: 4 vs 6 Headaches: 4 vs 7	5 withdrew: 2 from modafinil group and 3 from methylphenidate group Withdrawals due to AEs: NR	Tehran University of Medical Sciences	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Arnold 1978/Huestis 1975 (Fair)	Diagnosis of Minimal Brain Dysfunction with such signs an symptoms as hyperactivity, short attention span, distractibility, irritability, variability, explosiveness, aggression, inability to keep friends or function in a group, underachievement, visual-motor dysfunction, and poor coordination or other minor neurological signs; total score of 24 or more on the first six items of the David's Hyperkinetic Rating Scale, by parents and teacher; indication for stimulant treatment as determined by the patient's psychiatrist; aged between 5 and 12 years; enrollment in some sort of school setting to obtain teachers' ratings; no psychoactive drug in the preceding month; insufficient benefit from an initial 2-week "placebo washout" to be maintained without active drug	Days 1/2/3+: Dextroamphetamine: 5/10/15 mg Methylphenidate: 10/20/30 mg 3 weeks, then crossover Twice daily: morning and noon	NR	Mean age=8 75.9% male Race NR	Mean sum CTRS=91.52 CTRS factor I (conduct)=35.83 CTRS factor IV (hyperactivity)=23.10 Mean total items 1-6 DHRS by teachers=29.03 DHRS by teachers Item I (hyperactivity)=5.28 Mean total items 1-6 DHRS by parent=30.76 DHRS by parent Item I (hyperactivity)=5.24 Mean sum Problem Behavior Checklist by parent=190.07 Problem Behavior Checklist by parent factor I (aggression)/factor 4 (hyperactivity)=65.59/24.31 Target symptoms rating by psychiatrists=5.00	29	NR NR 29

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Arnold 1978/Huestis 1975 (Fair)	Mean changes on (p=NS for all): Conners' school behavior checklist by teachers: -21.26 vs -17.97 Sum of first 6 items on David's' Hyperkinetic Rating Scale by teacher: -6.65 vs -5.89 Item 7 (poor schoolwork) on David's' Hyperkinetic Rating Scale by teachers: -0.69 vs -0.79 First six items on David's' Hyperkinetic Rating Scale by parents: -5.45 vs -5.35 Problem checklist by parents: -43.1 vs -37.79 Psychiatrists' ratings of parent-assessed target symptoms: -1.87 vs -1.62	p=NS on all Poor appetite: -0.45 vs 0.35 Awake at night: 0.07 vs -0.03 Headaches: -0.27 vs -0.27 Tummy aches: -0.41 vs -0.31 Side effects of drug: 0.25 vs 0.25 Mean change in weight (kg): -1.32 vs -0.92; p=NS	NR NR	Grant from Ohio Department of Mental Health and Mental Retardation; matched dosage forms were furnished by Ciba-Geigy Pharmaceutical Corp.	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Barkley 2000 (Poor)	DSM-IV criteria for ADHD	Adderall 10 mg and 20 mg Methylphenidate 10 mg and 20 mg Placebo 1 week, then crossover Twice daily: morning and noon	NR	n=35 Mean age=14 85.7% male Race NR	Mean IQ=103.9	46	8 (17.4%) withdrawals/lost to fu NR/31 (89%) analyzed for parent/teen ratings; 13 (37%) analyzed from language arts teacher ratings; 15 (43%) analyzed from math teacher ratings; 33 (94%) analyzed from lab measures

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Barkley 2000 (Poor)	Mean scores for Adderall 5 mg/10 mg vs methylphenidate 5 mg/10 mg vs placebo: Parent ratings ADHD Total: 21.3/19.0 vs 21.01/16.8 vs 21.9 ODD Total: 10.0/8.2 vs 9.7/8.2 vs 9.4 Teen self-ratings ODD Total: 6.0/5.8 vs 5.6/5.2 vs 5.1 English Teacher ADHD Total: 21.9/18.1 vs 17.9/21.5 vs 22.5 ODD Total: 4.3/3.9 vs 5.2/5.0 vs 5.1 Math Teacher ADHD Total: 17.5/16.4 vs 12.2/14.0 vs 17.7 ODD Total: 4.7/6.1 vs 3.3/3.9 vs 4.8 In-clinic tests Stroop Word Score: 46.5/48.7 vs 46.3/49.5 vs 47.1 Stroop Color Score: 44.5/47.7 vs 45.2/46.2 vs 44.3 Stroop Interference: 52.0/54.8 vs 51.8/53.2 vs 49.7 CPT Omissions: 7.1/15.0 vs 15.5/23.2 vs 14.0 CPT Commissions: 15.2/13.8 vs 16.5/15.2 vs 15.7 CPT Reaction Time (ms): 391.0/408.1 vs 388.3/396.3 vs 417.2	Mean scores for Adderall 5 mg/10 mg vs methylphenidate 5 mg/10 mg vs placebo: Parent ratings Side effects number: 4.8/5.1 vs 5.4/5.5 vs 5.1 Side effects severity: 3.1/2.8 vs 3.0/2.9 vs 2.9 Teen self-ratings Side effects number: 4.7/4.7 vs 4.3/4.8 vs 4.6 Side effects severity: 2.5/2.4 vs 3.3/2.9 vs 2.7; "...teens rated the 10 mg dose of Adderall condition as producing significantly less severe side effects than the 5 mg dose of methylphenidate" English Teacher (n=13) 2.9/3.1 vs 3.2/3.6 vs 3.8 3.3/1.9 vs 3.4/2.7 vs 1.9 Math Teacher Side Effects Number: 3.1/3.9 vs 1.9/3.1 vs 3.2 Side Effects Severity: 2.6/2.3 vs 1.5/2.4 vs 2.2	NR NR	Shire	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Bédard 2015 US (Fair)	Participants were ages 6–17 years with DSM-IV diagnosis of ADHD (any subtype) and had participated in a larger crossover trial to evaluate comparative efficacy/tolerability and predictors of response to methylphenidate and atomoxetine. Comorbidity permitted provided ADHD was the primary disorder and the comorbid condition did not require medication treatment. Participants may have been treated with atomoxetine or methylphenidate but must not have been nonresponders or experienced disabling adverse effects of either medication.	A. Atomoxetine (ATX), mean final dose, SD: 1.4 (0.5) mg/kg. 2 or 3 capsules daily, determined by child's weight. B. OROS methylphenidate (MPH), mean final dose, SD: 52.4 (16.6) mg. 2 capsules daily. Titrated using a flexible, stepped dose optimization strategy in weekly sessions, based on assessment of clinical status and adverse effects, following a preestablished algorithm to a standard of no room for improvement. 4 dose levels for each drug (OROS MPH: 18 mg, 36 mg, 54 mg, 72 mg; ATX: 0.5 mg/kg, 1.0 mg/kg, 1.4 mg/kg, 1.8 mg/kg) Titrated in 4 - 6-week blocks separated by a 2-week placebo washout. Duration of study: 12 - 16 weeks.	Previous treatment with ATX or OROS MPH but 65% were treatment naïve.	Age, y: 10.5 ± 2.7 Gender, % female: 26 Ethnicity, n (%): African-American: 32 (31) Asian: 1 (1) Caucasian: 37 (36) Hispanic: 20 (20) Biracial/Other: 13 (12)	ADHD DSM-IV subtype, n (%): Inattentive: 37 (37) Hyperactive/Impulsive: 3 (3) Combined: 61 (60) Baseline ADHD-RS, mean (SD): Hyperactive/Impulsive total: 18.2 ± 7.3 Inattentive total: 22.0 ± 5.0 Comorbid ODD, n (%): 35 (34) Previously medicated, n (%): 36 (35)	102	25 discontinued at baseline assessment/16 during study/0 lost to follow-up/102 assessed
Bédard 2015 US (Fair) Continued.							

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Bédard 2015 US (Fair)	**ADHD-RS from pre- to post-treatment:** ATX, pre vs post: 36.55 ± 11.09 vs 20.54 ± 12.96, $t_{1,101}$ = 13.61, p < 0.001 MPH, pre vs post: 37.09 ± 10.96 vs 17.37 ± 11.29, $t_{1,101}$ = 17.27, p < 0.001 Changes from baseline in the ADHD-RS in any CPT measure: ATX (commission errors r = 0.08, omission errors r = 0.02, RT r = -0.06, RT variability r = -0.04) vs MPH (commission errors r = 0.02, omission errors r = 0.14, RT r = -0.2, RT variability r = 0.05) Changes from baseline in ADHD-RS inattention and hyperactivity/impulsivity subdomains were not significantly associated with changes in any CPT measure as a function of treatment with either medication (p > 0.05). **Commission errors:** Drug ($F_{1,101}$ = 0.001, p = 0.98, partial η^2 < 0.001) Time ($F_{1,101}$ = 2.28, p = 0.13, partial η^2 = 0.02) Drug x Time ($F_{1,101}$ = 0.04, p = 0.85, partial η^2 < 0.001) **Omission errors:** Drug x Time ($F_{1,101}$ = 4.61, p = 0.03, partial η^2 = 0.04) Time ($F_{1,101}$ = 6.47, p = 0.01, partial η^2 = 0.06) Drug ($F_{1,101}$ = 0.78, p = 0.38, partial η^2 = 0.01). Omission errors following treatment, post hoc paired t-tests, MPH vs ATX : p =.001 vs p = 0.69	Tolerability (see withdrawals) All other harms of interest: NR	**ATX vs MPH:** Total withdrawals*: 8 vs 8 Due to Tolerability: 2 vs 2 *Two withdrawals due to behavioral issues(noncompliance, hyperactivity) in MPH group vs 0 in ATX group.	NIMH, National Center for Research Resources, National Center for Advancing Translational Sciences of the NIH, and through a Canadian Institutes of Health Research Fellowship to primary author.	
Bédard 2015 US (Fair) Continued.	**Reaction time (RT):** Drug x Time ($F_{1,100}$ = 4.92, p = 0.03, partial η^2 = 0.05), MPH had a greater speeding of RT than ATX. Drug ($F_{1,100}$ = 0.015, p = 0.69, partial η^2 = 0.05) Time ($F_{1,100}$ = 4.90, p = 0.03, partial η^2 = 0.05) Post hoc paired t-test of RT, ATX p = 0.99 **Reaction time variability:** Time ($F_{1,101}$ = 20.07, p < 0.001, partial η^2 = 0.17) Drug ($F_{1,101}$ = 4.95, p = 0.03, partial η^2 = 0.05) Drug x Time ($F_{1,101}$ = 11.79, p = 0.001, partial η^2 = 0.104) Post hoc paired t-test of RT variability, ATX p = 0.17				

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Bergman 1991 US (Poor)	DSM-III diagnosis of Attention Deficit Disorder with Hyperactivity (ADDH)	Sustained-release methylphenidate 20 mg (single morning dose) Short-acting (regular) methylphenidate 10 mg (twice daily - morning and afternoon) Placebo 1 day	NR	Mean age NR (between 6 and 12) 100% male Ethnicity NR	NR	42	NR/NR/NR
Biederman 2006 StART substudy (Wigal 2005)	Subgroup of girls from Wigal 2005. See for eligibility criteria	See Wigal 2005	See Wigal 2005	Mean age=8.7 years Subgroup of 100% girls 59.1% white 22.8% black 17.5% Hispanic 1.8% Asian/pacific islander 8.8% other	Mean weight (lb): 71.98 ADHD subtype Hyperactive/impulsive: 0% Combined: 100%	57	NR/NR/57

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Bergman 1991 US (Poor)	SR methylphenidate = short-acting methylphenidate on all measures (data NR)	NR	NR NR	NIMH Grants (MH 38838-05 and MH 30906-09)	
Biederman 2006 StART substudy (Wigal 2005)	MAS XR vs atomoxetine SKAMP scale mean changes Deportment: -0.48 vs -0.04; p<0.001 Attention: -0.45 vs -0.05; p<0.001 Math problems (mean number) Attempted: 135.27 vs 119.72; p<0.04 Completed correctly: 94.4% vs 96%; NS	MAS XR vs atomoxetine (p-values NR) Appetite decrease: 40.7% vs 12.5% Upper abdominal pain: 29.6% vs 15.6% Insomnia: 25.9% vs 3.1% Headache: 14.8% vs 9.4% Weight decrease: 7.4% vs 0 Anorexia: 7.4% vs 6.3% Nausea: 3.7% vs 12.5% Vomiting: 3.7% vs 15.6% Somnolence: 3.7% vs 28.1% Fatigue: 0 vs 6.3% Any adverse event: 78% vs 66%	Overall withdrawals: NR AE withdrawals: 7% vs 3%	See Wigal 2005	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Biederman 2007 Lopez 2011 US (Fair)	Children 6-12 years old with DSM-IV-TR diagnosis of combined or predominantly hyperactive-impulsive subtype of ADHD. History of treatment with a stable regiment of stimulant medication, ability to follow classroom instructions, and functioning at age-appropriate academic levels	A: Lisdexamfetamine dimesylate (LDX) B: Mixed amphetamine salts extended-release (MAS XR) - reference arm Initial dose: 10mg/day 3-week open-label titration to optimal MAS XR dose (10, 20, or 30 mg/d); 3-week randomized, double-blind treatment crossover periods with optimum dose of MAS XR, LDX dose approximately equivalent to the optimized MAS XR dose, and placebo.	NR	Mean age: 9.1 years 63.5% male 55.8% White 23.1% Black 15.4% Hispanic 5.8% other	100% ADHD-combined subtype Mean age of ADHD onset: 5.8 years Mean time since diagnosis: 3.3 years Prior treatment Amphetamine: 44.2% Methylphenidate: 26.9% Stimulant NOS: 11.5% Stimulants with Atomoxetine: 9.6% Other: 1.9% Not listed: 5.8%	52	2 withdrew 1 was lost to follow-up 50 analyzed

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Biederman 2007 Lopez 2011 US (Fair)	**LS Mean SKAMP-DS scores at endpoint** LDX: 0.8 vs Placebo: 1.7 (p<0.0001) MAS XR: 0.8 vs Placebo: 1.7 (p<0.0001) **LS Mean SKAMP-AS scores at endpoint** LDX: 1.2 vs Placebo: 1.8 (p<0.0001) MAS XR: 1.2 vs Placebo: 1.8 (p<0.0001) **LS Means PERMP-A scores** LDX: 133.3 vs Placebo: 88.2 (p<0.0001) MAS XR: 133.6 vs Placebo: 88.2 (p<0.0001) **LS Means PERMP-C scores** LDX: 129.6 vs Placebo: 84.1 (p<0.0001) MAS XR: 129.4 vs Placebo: 84.1 (p<0.0001) **CGI-I scale at endpoint** LDX: 2.2 vs Placebo: 4.2 (p<0.0001) MAS XR: 2.3 vs Placebo: 4.2 (p<0.0001) Lopez, 2011 LDX vs. MAS XR vs. placebo Overall clinical improvement, LS mean (SD): 2.2 (0.2) vs. 2.3 (0.2) vs. 4.2 (0.2); p<0.0001 CGI-I scores at endpoint, ITT population, n (%): Improved or very much improved (CGI-I score=2 or 1): 37 (74) vs. 36 (72) vs. 9 (18) Improved (CGI-I score=2): 20 (42) vs. 28 (56) vs. NR Very much improved (CGI-I score=1): 16 (32) vs. 8 (16) vs. 1 (2) LDX showed significantly higher proportion of participants with a very much improved score vs. MAS XR (McNemar test: p=0.0386)	AEs occurring at an incidence of ≥ 2% during the double-blind period were: **LDX** Insomnia: 8% Decreased appetite: 6% Anorexia: 4% Upper respiratory infection: 2% **MAS XR** Decreased appetite: 4% Upper abdominal pain: 4% Upper respiratory infection: 2% Vomiting: 2% Insomnia: 2% **Placebo** Vomiting: 4% Insomnia: 2% Upper abdominal pain: 2% Lopez, 2011 LDX vs. MAS XR vs. placebo Titration period: Overall AE, %: NA vs. 46 vs. NA Insomnia, %: 10 Double-blind period: Overall AE, %: 16 vs. 18 vs. 15 AE with LDX: Insomnia, %: 8	2 withdrew 1 withdrew due to viral gastroenteritis	New River Pharmaceuticals and Shire Development Inc	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Borcherding 1990 (Poor)	DSM-III diagnosis of Attention Deficit Disorder with Hyperactivity (ADDH); medically healthy; WISC-R full scale IQ score > 80; score 2 SDs or above their age norms on Factor 4 (hyperactivity) of the CTRS	Mean dosages for weeks 1/2/3: Dexmethylphenidate 0.2/0.5/0.7 mg/kg Methylphenidate 0.5/0.8/1.3 mg /kg 3 weeks then crossover Twice daily: 9 a.m. and 1 p.m.	NR	Mean age=8.6 years 100% male 71.7% white, 2.2% black, 6.5% Hispanic/Asiatic	WISC-R Full Scale IQ=106.1 Mean CTRS for Factor 4 (hyperactivity)/Factor 1 (conduct): 2.5/1.2 28.3% stimulant naïve	46	1 (2.2%) withdrawn/lost to fu NR/# analyzed ranged by outcome

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Borcherding 1990 (Poor)	Efficacy NR	Abnormal movements Abnormal movements "NOTED": 34/45 (76%) overall Abnormal movements "OBSERVED": 27/34 (79%) Of those n=27 subjects (Dextroamphetamine vs methylphenidate; p=NS on all): Abnormal movements: 6 (22%) vs 10 (37%) Orofacial movements: 7 (27.9%) vs 7 (27.9%) Stereotypies: 2 (7.4%) vs 4 (14.8%) Compulsive behaviors Overall: 23/45 (51.1%) Of those 23 subjects (Dextroamphetamine vs methylphenidate; p=NS on all): Compulsive behaviors: 13 (56%) vs 5 (22%); p=0.09 STESS items (mean scores) Does things over & over a certain number of times before they seem quite right (n=38): 0.4 vs 0.4; both > placebo Meticulous; pays close attention to detail: 0.4 vs 0.3; both > placebo Overly neat and clean: 0.2 vs 0.1: only dextroamphetamine > placebo Has trouble making up his mind: 0.4 vs 0.5; methylphenidate > placebo Jerks/twitches or unusual movements: 0.2 vs 0.2; both = placebo CPRS items (mean scores) (all "both > placebo) Compulsive acts: 1.7 vs 1.5 Nervous habits & mannerisms: 1.8 vs 1.7 Obsessive thinking: 2.0 vs 2.0	1 (2.2%) withdrawals withdrawals due to adverse events NR	NR	Compares results of this 100% female trial to trial of 45 boys (Castellanos 1996)

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Castellanos 1997 US Subgroup of Elia 1991 (Poor)	(1) DSM-III-R criteria for Tourette's disorder with tics confirmed by a knowledgeable clinician at least 1 year prior to referral (Tourette Syndrome Classification Study Group, 1993); (2) symptoms of ADHD present in at least two settings; (3) Conners hyperactivity factor scores from their home teacher were at least 2 SD greater than age norms Tourette's syndrome	Group 1 (n=12), Low-medium-high Weeks 1, 2, and 3 for children < 30 kg/> 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg Placebo Group 2 (n=6), Low-medium-medium Weeks 1, 2, and 3 for children < 30 kg/> 30 kg: Dextroamphetamine 10, 25, and 25 mg/15, 30, and 30 mg Methylphenidate 25, 40 and 40 mg/30, 50 and 50 mg Placebo Group 3 (n=4), Low-high-high Weeks 1, 2, and 3 for children < 30 kg/> 30 kg: Dextroamphetamine 10, 40, and 40 mg/15, 45, and 45 mg Methylphenidate 25, 70 and 70 mg/30, 90 and 900 mg Placebo 3 weeks then crossover; BID at 9 am and 1 pm; individualized curriculum and instruction provided from 9am to 12:30pm in a highly structured classroom, including a positive reinforcement management program using play money (paid for appropriate behavior and fined for inappropriate behavior).	Haloperidol	Mean age=9.4 Gender NR 80% white	WISC-R Full Scale IQ=98.8 WISC-R Verbal=102 WISC-R Performance=95.6 Yale Global Tic Severity Scale (0-104)=37.3 CTRS Conduct/Hyperactivity factors=0.59/1.98 C-GAS=42.6	Group 1=22, Group 2=6, Group 3=4	# withdrawn: Group 1=2(9.1%), Group 2=nr, Group 3=n4/lost to fu NR/Analyzed: Group 1=20, Group 2=nr, Group 3=nr

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Castellanos 1997 US Subgroup of Elia 1991 (Poor)	Tic severity Dextroamphetamine had greater severity than placebo (+25%), p<0.05 Methylphenidate severity indistinguishable from placebo (-4%), p=NS	# cases with dextroamphetamine vs methylphenidate (denominate unclear) Marked appetite suppression with transient weight loss: 4 vs 3 Initial insomnia: 10 vs 2 Transient obsessive-compulsive symptoms: 1 vs 5	NR NR	NR	NIMH Research Day Program

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Chronis 2003/Pelham 1999a (Fair)	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a
Coghill 2013 Soutullo 2013 Banaschewski 2013 Coghill 2014 Europe (Fair)	Male and female children 6-17 y with DSM-IV-TR criteria for primary diagnosis of ADHD. At least moderate severity according to ADHD Rating Scale version IV total score of 28 or higher.	A: Lisdexamfetamine dimesylate (LDX) dose optimized (30, 50, or 70 mg/d) for 7 d B: Osmotic-release oral system methylphenidate dose optimized (18, 36, or 54 mg/d) for 7 d (OROS-MPH) C: Placebo (P) for 7 d	No other effective or tolerated ADHD Drugs	Age (mean), y: 10.9 Gender, % female: 19.3 Ethnicity, %: Hispanic: 1.2 Non-white: 3 Race, %: White: 97 Black/African American: 0.3 Asian: 0.3 Other: 2.4	ADHD subtype, %: Predominantly inattentive: 16 Predominantly hyperactive-impulsive: 3 Combined: 81 Previously treated with any ADHD medication, %: 54.8 Any concomitant psychiatric diagnosis, %: 20.5	336	139/1/317

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Chronis 2003/Pelham 1999a (Fair)	1) Placebo/Placebo/Placebo 2) MPH .3/.3/.3 3) MPH .3/.3/.15 4) MPH .3/Placebo/Placebo 5) Adderall .3/Placebo/.3 6) Adderall .3/Placebo/.15 7) Adderall .3/Placebo/Placebo All p-values reflect comparison to condition #1 (Placebo/Placebo/Placebo) Positive affect (all p=NS): 1) 28.1; 2) 30.81; 3) 29.17; 4) 29.40; 5) 30.28; 6) 30.29; 7) 29.62 Negative affect (all p=NS): 1) 12.51; 2) 11.43; 3) 12.67; 4) 12.22; 5) 11.90, 6) 11.68, 7) 11.79 Parent task completion (all p=NS): 1) 2.34; 2) 1.94; 3) 2.18; 4) 2.29; 5) 2.25; 6) 1.95; 7) 2.37 Child task completion: 1) 2.46; 2) 1.61, **p<0.01**; 3) 2.47; 4) 2.17; 5) 1.78; 6) 1.77, **p<0.01**; 7) 2.17 Overall effectiveness: 1) 2.52; 2) 1.90, **p<0.01**; 3) 2.27; 4) 2.19; 5) 2.07; 6) 1.75, **p<0.001**; 7) 2.22 Pleasantness of interaction: 1) 2.76; 2) 1.65, **p<0.01**; 3) 2.41; 4) 2.26, **p<0.01**; 5) 1.67, **p<0.01**; 6) 1.44, **p<0.001**; 7) 1.98, **p<0.01**	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	
Coghill 2013 Soutullo 2013 Banaschewski 2013 Coghill 2014 Europe (Fair)	Coghill, 2013 LDX vs. OROS-MPH Proportions of patient with change of CGI-I rating of 1 (very much improved) or 2 (much improved): 78% vs. 61% LS mean change in ADHD-RS-IV total score (SE): -24.3 (1.2) vs. -18.7 (1.1) LS mean change in ADHD-RS-IV subscores Inattention*: -13.0 vs. -10.5 Hyperactivity/impulsivity*: -11.0 vs. -9.0	Coghill, 2013 LDX vs. OROS-MPH, no. (%) Any AE: 80 (72.1) vs. 72 (64.9) SAE: 3 (2.7) vs. 2 (1.8) Decreased appetite: 28 (25.2) vs. 17 (5.3) Insomnia: 16 (14.4) vs. 9 (8.1) Anorexia: 12 (10.8) vs. 6 (5.4)	Coghill, 2013 LDX vs. OROS-MPH, no. (%) Total withdrawals (due to lack of efficacy): 11 (9.7) vs. 22 (19.6) Withdrawals due to AE: 5 (4.5) vs. 2 (1.8)	Shire Development LLC	*data approximated from figure **based on normative data ***effect size = difference in LS mean divided by root-mean-square error.

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Coghill 2013 Soutullo 2013 Banaschewski 2013 Coghill 2014 Europe (Fair) Continued.							

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Coghill 2013 Soutullo 2013 Banaschewski 2013 Coghill 2014 Europe (Fair) Continued.	Soutullo, 2013 LDX minus P vs. OROS-MPH minus P vs. LDX minus OROS-MPH LS mean difference in ADHD-RS-IV total score: -18.6; (p<0.001; 95% CI, -21.5 to -15.7; effect size, 1.80) vs. -13.0 (p<0.001; 95% CI, -15.9 to -10.2; effect size, 1.26) vs. -5.6 (p<0.001; 95% CI, -8.4 to -2.7; effect size, 0.54) Proportions of patient with change of CGI-I rating of 1 (very much improved) or 2 (much improved): 63.6% (p<0.001; 95% CI, 53.0 to 74.1) vs. 46.2% (p<0.001; 95% CI, 34.6 to 57.7) vs. 17.4 (p<0.05; 95% CI, 5.0 to 29.8) Responders (≥30% reduction from baseline ADHD-RS-IV total score and CGI-I of 1 or 2): 63.5% (p<0.001; 95% CI, 53.0-74.1) vs. 45.2% (p<0.001; 95% CI, 33.9 to 56.5) vs. 18.3 (p<0.05; 95% CI, 5.4-31.3) Responders (ADHD-RS-IV total score ≤ mean for age**): 50.6% (p<0.001; 95% CI, 39.0 to 62.1) vs. 36.5 (p<0.001; 95% CI, 24.8 to 48.3) vs. 14.0 (p=0.050; 95% CI, 0.6 to 27.4)				

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Coghill 2013 Soutullo 2013 Banaschewski 2013 Coghill 2014 Europe (Fair) Continued.							
Coghill 2013 Soutullo 2013 Banaschewski 2013 Coghill 2014 Europe (Fair) Continued.							

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Coghill 2013 Soutullo 2013 Banaschewski 2013 Coghill 2014 Europe (Fair) Continued.	Banaschewski, 2013 LDX vs. OROS-MPH LS mean change in CHIP-CE:PRF domain T-scores from baseline to end-point* Achievement: 9 (95% CI, 7 to 11) vs. 6 (95% CI, 4.0 to 7.0) Risk Avoidance: 10 (95% CI, 8 to 12) vs. 9 (95% CI, 6.0 to 11) Resilience: 3.5 (95% CI, 0.5 to 5) vs. 2.5 (95% CI, 0.1 to 5.0) Satisfaction: 4 (95% CI, 0.1 to 4) vs. 3.5 (95% CI, 0.1 to 5.0) Comfort: 2 (95% CI, 0.1 to 4.5) vs. 4 (95% CI, 3.0 to 5.1) LS Mean change in WFIRS-P domain and total scores from baseline to endpoint* Family: -3.8 (95% CI, -2.1 to -5.5) vs. -3.5 (95% CI, -0.19 to -0.5) Learning and School -0.5 (95% CI, -0.4 to -0.65) vs. -0.4 (95% CI, -0.25 to -0.5) Life Skills -0.1 (95% CI, 0.05 to -0.2) vs. -0.15 (95% CI, -0.05 to -0.25) Child's self concept: -0.18 (95% CI, 0.05 to -0.38) vs. -0.21 (95% CI, -0.75 to -0.45) Social activities: -0.275 (95% CI, -0.17 to -0.39) vs. -0.25 (95% CI, -0.17 to -0.39) Risky activity: -0.18 (95% CI, -0.15 to -0.25) vs. -0.1 (95% CI, -0.05 to -0.2) Total: -0.3 (95% CI, -0.19 to -0.39) vs. -0.25 (95% CI, -0.17 to -0.37)				*approximated from a figure
Coghill 2013 Soutullo 2013 Banaschewski 2013 Coghill 2014 Europe (Fair) Continued.	Coghill, 2014 LDX vs. OROS-MPH Difference in least square mean, Conners' Parent Rating Scale-Revised (CPRS-R) total scores by study visit, difference in LS mean change from baseline*: -24.5 vs. -19.0 CPRS-R total score by time of day (1000h/1400h/1800h), LS mean change (95% CI), p-value, effect size*** LDX vs. OROS-MPH: -5.8 (95% CI, -10.3 to -1.4)/-6.8 (95% CI, -11.4 to -2.3)/-6.1 (95% CI, -10.9 to -1.4); p<0.05, 0.377				*approximated from a graph

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Connor 2000 US (Poor)	Children aged 6-16 years meeting DSM-III-R criteria for ADHD and either Aggressive Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD) with a score of 1.5 standard deviations above the mean for age and gender on the Parent Child Behavior Checklist (CBCL) Attention Problems Scale and a score on the Teacher Child Attention Problem Rating Scale (CAPS) of at least the 93rd percentile.	A: Clonidine maximum, flexibly titrated based on clinical efficacy and reported side effects, of 0.3 mg three times daily (mean dose 0.17 mg/d) B: Methylphenidate maximum, flexibly titrated based on clinical efficacy and reported side effects, of 40 mg twice daily (mean dose 32.5 mg/d) Titration periods at 1, 2, and 3 months time periods where dosage assessments were conducted. Duration of study: 3 months.	All were free of medication at baseline.	Age: 9.1 years Gender NR 23 (96%) White 1 (4%) African American	11 (46%) had history of receiving MPH prior to study. No child had a previous treatment history with any other psychiatric medication.	24	0/0/24

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Connor 2000 US (Poor)	Clonidine only vs Methylphenidate only **Parent Ratings** No interaction was found to be significant for group X time. **Teachers Ratings** SSQ Number of Problem Settings 7.3 at month 3 vs 3.1 at month 3 (p= 0.009) APRS Group receiving MPH only was significantly improved at all time points in comparison to the clonidine only group (p=0.02). Time point values NR. **Laboratory Scores** GPB Marginally significant finding for time score for non-dominant hand in clonidine only group (F= 2.50, p=0.068). Time point values NR. No significant effects were found for non-dominant hand number of errors. 1.0 errors at 2 months and 3 months vs 0.1 errors at 2 months and 0.23 errors at 3 months for number of errors for dominant hand performance. This was significant, but P value NR. Marginally significant effect for clonidine group with slower completion times with the dominant hand than the MPH group (F=2.22, p=0.052).	No differences over time were found for number of parent-reported side effects. Parents reported a decreasing mean of severity of side effects with time across all 3 groups.	Clonidine vs Methylphenidate Total withdrawals: 2 (25%) vs 1 (12.5%) Due to AE: 0 (0%) vs 1 (12.5%)	UMMS Small Grants Project Award	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Cox 2004 (Fair)	Diagnosis of current ADHD as determined by parent-report questionnaire and structured clinical interviews (DuPaul ADHD Rating Scale-IV, Diagnostic Interview Schedule for Children, Standardized Interview for Adult ADHD; positive history of MPH responsiveness disclosed by subject and parent reports; and current daily driving activity	Methylphenidate in equal doses at 8 am, noon, and 4 pm (mean = 60 mg) Methylphenidate osmotic, controlled-release oral formulation (OROS) at 8 am (mean=54 mg) 7 days of dosage maintenance	NR	Mean age =17.2 100% male Race NR	Inattentive type=4(66.7%) Combined type=2(33.3%) Proportion taking medication for ADHD at baseline NR Mean baseline dose of MPH NR	7	1 (14.3%) withdrawn/0 lost to fu/analyzed=6

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Cox 2004 (Fair)	OROS Methylphenidate vs methylphenidate TID IDS 2 PM: -0.55 vs -0.54, p=NS 5 PM: -2.2 vs -1.04, p=NS 8 PM: -1.98 vs 4.23, p=0.01 11 PM: -1.65 vs 5.1, p=???? (wrote to author - reported as 0.1 in text but I think that's wrong) Individual parameters (F-value/p-value for MPH TID vs MPH OROS) Standard deviation steering: F=0.65, p=0.42 Off Road: 2.50/0.12 Veering across midline: 2.11/0.15 Inappropriate braking: 4.47/0.04 % missed stop signals: 5.76/0.02 % bumps: 1.35/0.25 % crashes: 3.13/0.08 Speeding: 1.60/0.21 Standard deviation speed: 4.19/0.04 Risky Driving Means (daily driving diaries - self reported): 2.6 vs 3.2, p=NS	NR	1 (14.3%) withdrawals 0 due to adverse events	McNeil Consumer and Specialty Pharmaceuticals	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Cox 2006	Male and female active drivers who had ADHD and were aged 16 to 19 years were eligible to participate in the study. To be included in the study, adolescents had to have a diagnosis of current ADHD as determined by parent report, questionnaire, and structured clinical interviews; a positive history of stimulant responsiveness as disclosed by adolescents and parent reports; and current license to drive and reported daily driving activity. Adolescents were excluded when they had a history of tics or any adverse reactions to stimulant medication, a history of substance abuse disclosed by patient or parent, or a coexisting medical condition or medication usage that is known to interfere with the safe administration of stimulant medications.	OROS MPH, se-AMPH ER, or placebo Days 1 through 5, a half dose (36 mg/day OROS MPH or 15 mg/day se-AMPH ER), and on days 6 to 17, the full study dose of active drug (72 mg/day of OROS MPH or 30 mg/day of se-AMPH ER).	21 were taking MPH , and 12 were taking amphetamine formulations.	Mean Age 17.8 yrs Gender: 54% male Ethnicity: NR	Medication before study No medication 2 MPH formulations 21 Amphetamine formulations 12	35	35 analyzed

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Cox 2006	Overall driving performance was better with active treatment. a significant medication effect vs. placebo (F = 7.16, P < 0.001). Separate contrasts demonstrated that OROS MPH was associated with better driving performance than placebo (t = 3.31, P = .001) and se-AMPH ER (t = 2.15, P = 0.03), se-AMPH ER was not associated with better driving than placebo (t = 1.17, P < 0.24)	One AE reported OROS MPH 36 urinary difficulty	No withdrawals but two participants rescheduled due to lack of adherence	McNeil Pediatrics Division of McNeil-PPC, Inc.	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Dittmann 2013 US, Canada, 7 European Countries NCT01106430 (Fair)	Patients aged 6–17 y who satisfied DSM-IV-Text Revision criteria for a primary diagnosis of ADHD of at least moderate severity as shown by a baseline ADHD Rating Scale IV (ADHD-RS-IV) total score of 28 or higher.	A. Lisdexamfetamine dimesylate (LDX) 30, 50 or 70 mg QD B. Atomoxetine (ATX) QD for patients <70 kg, 0.5–1.2 mg/kg not to exceed 1.4 mg/kg; patients ≥70 kg, 40, 80 or 100 mg. Drug dosage was titrated from Baseline to Week 3 until an 'acceptable' response was achieved, 30% reduction from Baseline in the ADHD-RS-IV total score and a CGI-I score 1 or 2 with tolerable side effects. Duration of study: 9 weeks.	NR	Age (mean), y: 10.65 Gender, % female: 25 Ethnicity, %: Hispanic or Latino: 19 Not Hispanic or Latino: 81	LDX vs ATX: CGI-S score at baseline, mean (SD): 5.0 (0.80) vs 5.0 (0.73) ADHD-RS-IV total score at baseline, mean (SD): 42.6 (6.14) vs 41.9 (6.70) ADHD subtype, %: Predominantly inattentive: 17.2 vs 16.4 Predominantly hyperactive-impulsive: 1.6 vs 5.2 Combined: 81.3 vs 78.4 Concomitant psychiatric diagnosis, %: Any: 21.1 vs 17.2 Oppositional defiant disorder: 10.2 vs 9.7	267	12/6/262
Dopfner 2004 Germany Designed as a non-inferiority trial	Children between 8 and 15 years who met ICD-10 diagnosis of Hyperkinetic Disorder (F90) of a DSM-IV diagnosis of ADHD using a diagnostic checklist, DCL-HKS. All patients were methylphenidate responders on the basis of clinical assessment. They also had to have an intelligence IQ ≥85 and a body weight >20 kg.	Medikinet-Retard (methylphenidate ER) QD Methylphenidate IR (MPH IR) bid Placebo Dosage varied: 9 patients (11%) received 10 mg/d; 54 (68%) patients received 20 mg/d; 14 patients (17%) received 30 mg; and 2 patients (3%) received 40mg.	NR	Mean age: 10.0 yrs Gender: 89.9% male Ethnicity NR	Mean IQ: 103.0 (+/- 10.4) DSM-IV diagnosis of ADHD Combined type: 92.4% Predominately inattentive: 7.6%	82	3/ NR/ 79

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Dittmann 2013 US, Canada, 7 European Countries NCT01106430 (Fair)	LDX vs ATX: Median time to first clinical response (CGI-I 1 or 2): 12.0 days (95% CI, 8.0–16.0) vs 21.0 days (95% CI, 15.0–23.0), p=0.001 % responding to treatment by week 9: 81.7 % (95% CI, 75.0–88.5) vs 63.6 % (95% CI, 55.4–71.8), p=0.001 Change from baseline in ADHD-RS-IV total score by visit 9, mean (SD): -26.3 (11.94) vs -19.4 (12.82) ADHD-RS-IV total score LDX and ATX difference in least-squares mean change from baseline: -6.5 (95% CI, -9.3 to -3.6); p<0.001; effect size 0.56 Inattentiveness subscale score: -3.4 (95% CI, -4.9 to -1.8); p<0.001; effect size 0.53 Hyperactivity/impulsivity subscale score: -3.2 (95% CI, -4.6 to -1.7); p<0.001; effect size 0.53	LDX vs ATX, %: Any treatment-emergent adverse events (TEAEs): 71.9 vs 70.9 Any serious TEAE: 0 vs 0 Any TEAE leading to discontinuation of study drug: 6.3 vs 7.5 Insomnia: 11.7 vs 6.0 Anorexia/decreased appetite: 25.8 vs 10.4 Decreased weight: 21.9 vs 6.7 Abuse potential, tics, anxiety and sexual dysfunction: NR	LDX vs ATX, no.: Total withdrawals: 33 vs 33 Due to TEAE/Adverse Event: 8 vs 10	Shire	
Dopfner 2004 Germany Designed as a non-inferiority trial	Results of repeated measures analysis of variance of SKAMP and PERMP scores, Treatment effect: SKAMP attention: F 2.77 = 27.4, p<0.000 SKAMP deportment: F 2.77 = 18.8; p<0.000 PERMP no. attempted: F 2.77 = 17.8; p<0.000 PERMP no. correct: F 2.77 = 17.2; p<0.000	NR	NR	Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, D-58638 Iserlohn	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Efron 1997 Australia (Fair)	Age between 5 and 15 years; meet DSM-IV criteria for ADHD. The DuPaul ADHD rating scale was used; each DSM-IV ADHD symptom was marked on a 4-point scale: "never or rarely," (0); "sometimes," (1); "often," (2); and "very often," (3). Only symptoms rated 2 or 3 were considered present and counted toward the diagnosis; T-score of at least 1.5 standard deviations (SD) above the mean on the Attention Problems scale of the Child Behavior Checklist or Teacher Report Form. No history of intellectual disability, gross neurologic abnormality, or Tourette's syndrome. Decision made to trial stimulant medication on clinical grounds.	Dextroamphetamine 0.15mg/kg Methylphenidate 0.3 mg/kg Both rounded off to the nearest capsule size x 2 weeks then crossover	NR	8.7 years NR NR	ADHD-mixed type=101(81.8%) ADHD-predominantly inattentive=22(17.6%) ADHD-predominantly hyperactive/impulsive=2(1.6%) Mean IQ=98.9	125	NR NR 125

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Efron 1997 Australia (Fair)	% subjects rated by their parents as improved overall compared with their usual selves: 86 (68.8%) vs 90 (72%); p=NS (CTRS-R and CPRS-R data generally corroborated with these proportions of global response to the two stimulants)	Trouble sleeping: 88(70%) vs 79(64%), p=NS Poor appetite: 74(59%) vs 69(56%), p=NS Irritable: 102(82%) vs 100(80%), p=NS Proneness to crying: 95(76% vs 89(71%), p=NS Anxiousness: 85(68%) vs 76(61%), p=NS Sadness/unhappiness: 74(59%) vs 69(56%), p=NS Headaches: 38(30%) vs 30(24%), p=NS Stomachaches: 50(40%) vs 40(32%), p=NS Nightmares: 35(28%) vs 26(21%), p=NS Daydreams: 78(62%) vs 77(62%), p=NS Talking little with others: 37(30%) vs 35(28%), p=NS Uninterested in others: 43(34%) vs 39(31%), p=NS Drowsiness: 23(18%) vs 22(18%), p=NS Biting fingernails: 50(405) vs 56(45%), p=NS Unusually happy: 33(26%) vs 35(28%), p=NS Dizziness: 18(14%) vs 15(12%), p=NS Tics or nervous movements: 32(26%) vs 35(28%), p=NS Severity: dexamphetamine > methylphenidate on trouble sleeping, irritability, prone to crying, anxiousness, sadness/unhappiness, nightmares (data NR)	Total withdrawals NR Withdrawals due to adverse events: 2(1.6%) vs 2(1.6%)	NR	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Efron 1998 Australia (Fair)	Age between 5 and 15 years; meet DSM-IV criteria for ADHD. The DuPaul ADHD rating scale was used; each DSM-IV ADHD symptom was marked on a 4-point scale: "never or rarely," (0); "sometimes," (1); "often," (2); and "very often," (3). Only symptoms rated 2 or 3 were considered present and counted toward the diagnosis; T-score of at least 1.5 standard deviations (SD) above the mean on the Attention Problems scale of the Child Behavior Checklist or Teacher Report Form. No history of intellectual disability, gross neurologic abnormality, or Tourette's syndrome. Decision made to trial stimulant medication on clinical grounds.	Dextroamphetamine 0.15mg/kg Methylphenidate 0.3 mg/kg Both rounded off to the nearest capsule size x 2 weeks then crossover	NR	Mean age= 9.3 years 91.2% male Race NR	ADHD-Mixed type=84(82.4%) ADHD-predominantly inattentive=17(16.7%) ADHD-predominantly hyperactive/impulsive=1(1%) Mean IQ=98.8 Learning disability for reading=30(27.3%) Learning disorder for spelling=36(32.7%)	102	NR NR 102
Elia 1990 US (Fair)	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, school, or hospital). A score 2 SD or more above age norms was required on Factor IV (hyperactivity) of the revised 39-item Conners Teacher Rating Scale(CTRS). WISC-R Full scale IQ score of 80 or more	Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg 3 weeks then crossover Twice daily at 9 am and 1 pm	NR	Mean age=8.5 years 100% male Race NR	Mean Full Scale WISC-R IQ=102 Mean CTRS factor I (conduct)/factor IV (hyperactivity): 1.3/2.6 Mean CPRS factor I (conduct)/factor IV (hyperactivity): 1.6/2.4 Stimulant naïve: 18 (37.5%)	31	NR NR NR

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Efron 1998 Australia (Fair)	Dextroamphetamine versus methylphenidate: Child's rating: "When I took this medication I felt:" (cases/%) Much worse than usual: 6/5.9 vs 5/4.9 Worse than usual: 13/12.9 vs 8/7.8 About the same as usual: 26/25.7 vs 25/24.5 Better than usual: 23/22.8 vs 35/34.3 Much better than usual: 33/32.7 vs 29/28.4 Child's rating: "How helpful was the medication?" (cases/%) Very helpful: 39/38.6 vs 46/45.1 A bit helpful: 25/24.8 vs 29/28.4 Not sure: 27/26.7 vs 15/14.7 Not very helpful: 5/5 vs 4/3.9 Not at all helpful: 5/5 vs 8/7.8	NR	NR NR	NR	
Elia 1990 US (Fair)	dextroamphetamine=methylphenidate on all measures (limited data provided in graph format) Estimated from graphs (dextroamphetamine vs methylphenidate) <u>Mean changes in (all p=NS):</u> CGI: +2.5 vs +2.8 CPT (# correct): +9 vs +10 CTRS Factor I: -0.4 vs -0.4; CTRS Factor IV: -0.8 vs -0.8 CPRS Factor I: -0.7 vs -0.6; CPRS Factor IV: -1.2 vs -1	NR	NR NR	NR	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Elia 1991/Schmidt 1994 US (Fair)	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, school, or hospital). A score 2 SD or more above age norms was required on Factor IV (hyperactivity) of the revised 39-item Conners Teacher Rating Scale(CTRS). Parents also completed the 48-item Conners Parent Questionnaire (CPQ).	Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg 3 weeks then crossover Twice daily at 9 am and 1 pm	NR	Mean age=8.6 years 100% male	Mean Full Scale WISC-R IQ=105.6 Mean CTRS factor I (conduct) - teacher/parent rating: 1.3/1.5 Mean CTRS factor IV (hyperactivity) - teacher/parent rating: 2.6/2.4 Stimulant naïve: 18 (37.5%)	48	NR NR NR
Elia 1993 US (Fair)	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, school, or hospital). A score 2 SD or more above age norms was required on Factor IV (hyperactivity) of the CTQ-R. A WISC-R full scale IQ score > 80.	Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg Placebo 3 weeks then crossover Twice daily at 9 am and 1 pm Individualized curriculum and instruction provided from 9 am to 12:30 pm in a *highly structured classroom*. This included a positive reinforcement management program using play money. Children were paid for appropriate behavior and fined for inappropriate behavior.	NR	Mean age= 9.3 years Gender NR	Mean Full Scale WISC-R IQ=108.8 Mean CTQ-R factor I (conduct)=1.16 Mean CTQ-R factor IV (hyperactivity)=2.49 Mean CPQ-R factor I (conduct)=1.49 Mean CPQ-R factor IV (hyperactivity)=2.26	33	NR/NR/33

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Elia 1991/Schmidt 1994 US (Fair)	dextroamphetamine=methylphenidate on all measures (limited data provided in graph format) Estimated from graphs (dextroamphetamine vs methylphenidate) <u>Mean changes in (all p=NS):</u> CGI: 2.3 vs 2.4; GAS: 5 vs 6 39-item Conners Factor I (conduct): -0.41 vs -0.41 48-item Conners Factor I (conduct): -0.5 vs -0.39 CPT (# omission errors): -11 vs -11 39-item Conners Factor IV (hyperactivity): -0.9 vs -1 48-item Conners Factor IV (hyperactivity): -1.2 vs -1.0 CPT (# commission errors): -13 vs -14	dextroamphetamine vs methylphenidate (% patients with mild/moderate/severe severity scores on STESS) (all p=NS) Decreased appetite (n=48): 40/42/13 vs 40/35/10 Sleep difficulties (n=48): 31/40/10 vs 40/31/8 Overly meticulous (n=33): 18/12/6 vs 30/3/0 Not happy (n=48): 25/33/4 vs 27/35/6 dextroamphetamine vs methylphenidate (% patients with mild/moderate/severe severity scores on CPRS) (p=NS) Nervous habits and mannerisms: 35/9/0 vs 26/21/3	NR NR	NR	
Elia 1993 US (Fair)	<u>Combined Reading Scores</u> *Percent correct* Dextroamphetamine vs placebo=89.5 vs 86.1; p<0.01 Methylphenidate vs placebo=89.7 vs 86.1; p<0.01 *Mean number of attempts* Dextroamphetamine vs placebo=11.4 vs 9.5; p<0.01 Methylphenidate vs placebo=10.6 vs 9.5; p<0.01 Dextroamphetamine vs methylphenidate: p<0.05 <u>Combined Arithmetic Scores</u> *Percent correct* Dextroamphetamine vs placebo=97.1 vs 94.0; p<0.05 Methylphenidate vs placebo=96.2 vs 94.0; p=NS *Mean number of attempts* Dextroamphetamine vs placebo=38.3 vs 30.5; p<0.01 Methylphenidate vs placebo=39.2 vs 30.5; p<0.05	% patients (dextroamphetamine vs methylphenidate) Decreased appetite: 43 vs 46 Difficult with sleeping: 42 vs 36 Overly meticulous behavior: 24 and 21 Seemed unhappy: 12 vs 24 Transient tics or other nervous mannerisms: 36 vs 39	Withdrawals due to adverse events: 0 vs 0	NR	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Findling 2006 Australia, Canada, US (Fair)	Children aged 6–12 years were eligible to participate if they met diagnostic criteria for one of the three subtypes of ADHD as described in the Diagnostic & Statistical Manual of Mental Disorders, 4th Edition and had been on a stable dose of MPH for at least 3 weeks prior to screening. The diagnosis of ADHD was confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children— Present and Lifetime version (K-SADS-PL). Inclusion Criteria: Male and female children aged 6–12 years (inclusive); On a stable dose of methylphenidate ≥3 weeks prior to screening; diagnosed with ADHD based on DSM-IV criteria for any subtype and confirmed by administration of the K-SADS-PL interview at screening; attending a school setting in which a single teacher could make morning and afternoon assessments of the child's behavior.	Mean Dose: NR MPH-IR twice-daily (morning and lunch-time), EqXL once-daily (morning) followed by placebo at lunch-time, or placebo twice-daily (morning and lunch-time) for 3 weeks. The dosages of the active treatments were determined according to the child's pre-study MPH regimen: Children on a previous total daily dose of 10–20 mg IR MPH or 20 mg ER MPH were randomized to receive either 10 mg MPH-IR twice-daily, 20 mg EqXL once-daily, or placebo; children on a previous total daily dose of 25–40 mg IR MPH or >20 mg to £40 mg ER MPH were randomized to receive 20 mg MPH-IR twice-daily, 40 mg EqXL once-daily, or placebo; and children on a previous total daily dose >40 mg IR MPH or >40 mg ER MPH were randomized to receive 30 mg MPH-IR twice-daily, 60 mg EqXL once-daily or placebo.	NR	Mean age=9.5 yrs (Range=6-12 yrs) 79.2% male 85.8% Caucasian 5.3% Afro-Caribbean 0.3% Asian 1.6% Hispanic 6.9% other	ADHD Subtype: Inattention: 23% Hyperactive/Impulsivity: 5.7% Combined subtype: 71.4%	327 (318 received treatment)	9 withdrawn due to failure to meet all eligibility criteria 318 analyzed

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Findling 2006 Australia, Canada, US (Fair)	Difference from placebo (95% CI) for MPH-IR vs EqXL Teacher's Ratings: I/O component of 10-item IOWA Conners' Rating Scale 1-week: -2.4 (-3.36, -1.39) vs -1.9 (-2.87, -0.91) 2-week: -2.6 (-3.70, -1.43) vs. -2.4 (-3.58, -1.31) 3-week: -3.4 (-4.53, -2.26) vs. -3.1 (-4.26, -2.00) Teacher's Ratings: O/D component of 10-item IOWA Conners' Rating Scale 1-week: -1.7 (-2.54, -0.38) vs. -1.5 (-2.32, -0.62) 2-week: -1.9 (-2.81, -0.93) vs. -1.8 (-2.69, -0.81) 3-week: -2.4 (-3.36, -1.38) vs. -2.5 (-3.47, -1.48) Parent's Ratings: I/O component of 10-item IOWA Conners' Rating Scale 1-week: -2.3 (-3.31, -1.22) vs. -1.3 (-2.33, -0.23) 2-week: -2.6 (-3.65, -1.53) vs. -1.9 (-2.97, -0.86) 3-week: -3.0 (-4.09, -1.85) vs. -1.7 (-2.78, -0.54) Parent's Ratings: O/D component of 10-item IOWA Conners' Rating Scale 1-week: -2.1 (-3.22, -1.04) vs. -1.8 (-2.89, -0.71) 2-week: -2.5 (-3.64, -1.30) vs. -2.1 (-3.26, -0.92) 3-week: -2.3 (-3.46, -1.16) vs. -1.6 (-2.74, -0.44)	Adverse events occurring in ≥ 3% of patients [placebo (n=46) vs. MPH-IR (n=133) vs. EqXL (n=139)]: Headache: 4.3% vs. 13.5% vs. 18.0% (p=0.059) Anorexia: 0 vs. 3.0% vs. 6.5% (p=0.131) Abdominal pain, upper: 6.5% vs. 6.8% vs. 5.8% (p=0.951) ADHD: 34.8% vs. 4.5% vs. 5.8% (p<0.001) Nasopharyngitis: 6.5% vs. 1.5% vs. 5.8% (p=0.098) Insomnia: 0 vs. 3.8% vs. 4.3% (p-0.497) Decreased appetite: 0 vs. 2.3% vs. 3.6% (p=0.564) Pyrexia: 6.5% vs. 0.8% vs. 2.9% (p=0.077) Vomiting NOS: 4.3% vs. 3.0% vs. 2.2% (p=0.657) Irritability: 2.2% vs. 3.8% vs. 1.4% (p=0.499)	33/318 (10.4%) withdrew before study completion 21/318 (6.6%) withdrew due to adverse events 9/327 post randomization exclusions	Celltech Americas, Inc	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Findling 2008 US (Fair/Poor)	Patients were aged 6-12 years, who were diagnosed with ADHD according to the DSM-IV-TR. Participants had a Kaufman Brief Intelligence Test IQ score of ≥80, a total score of ≥26 on the ADHD-RS-IV while unmedicated, and normal lab parameters and vital signs. Patients were excluded if they had any comorbid psychiatric diagnosis; a history of seizures during the last 2 years; a tic disorder; or any concurrent illness or skin disorder that might compromise safety or the study assessments.	Methylphenidate Transdermal System (MTS) Initial dose: 10mg/9 hour (range: 10-30mg) Methylphenidate Oral System (MOS) Initial dose: 18mg (range: 18-54mg) Placebo	NR	Mean age: 8.8 years 66.3% males 77.3% Caucasian 14.5% African American 0.7% Asian 7.5% other	ADHD Subtype Combined: 227 (80.5%) Inattentive: 48 (17.0%) Hyperactive/impulsive: 4 (1.4%) Unclassified: 3 (1.1%)	282	113 withdrew total; 8 after randomization but prior to receiving medication; 27 in MTS group vs 25 in MOS group vs 53 in Placebo group 4 lost to follow-up 274 analyzed
Fitzpatrick 1992 (Poor)	Diagnosis of ADD in the Diagnostic Instrument for Childhood and Adolescence (DICA)	Per-protocol dosages for patients < 30 kg / > 30 kg / mean dosages: Placebo Sustained-release (SR) methylphenidate 20 mg am / 20 mg am / mean=20 mg Standard (SA) methylphenidate: 7.5 mg in am and pm / 10 mg in am and pm / mean=17.1 mg Combination SA + SR methylphenidate: 5 mg SA+20 mg SR in am and 5 mg SA in pm / 7.5 SA + 20 mg SR in am and 7.5 mg SA in pm / mean=20 mg SR + 11.8 mg SA Each phase lasted 2 weeks	NR	Mean age=8.71 89.5% male Race NR	Weight=31.45 kg Wechsler Scale IQ=114.11 Peabody Individual Achievement Scale=105.68 Conners Hyperactivity Index-Parent/Teacher: 1.79/1.74 IOWA Inattention-Overactivity-Parent/Teacher=2.01/2.09 IOWA Aggression/Noncompliance-Parent/Teacher: 1.27/1.18 TOTS Aggression-Parent/Teacher: 0.88/0.72 TOTS Hyperactivity-Parent/Teacher=0.86/0.56 TOTS Attention Parent/Teacher=0.32/0.46	19	NR/NR/NR

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Findling 2008 US (Fair/Poor)	ADHD-RS-IV Total Score (MTS vs MOS vs Placebo) Baseline: 43.0 vs 43.8 vs 41.9 Endpoint: 18.8 vs 21.8 vs 32.1 (p<0.0001 for both interventions vs placebo, no difference between treatment groups) CTRS-R Total Score (MTS vs MOS vs Placebo) Baseline: 34.9 vs 34.9 vs 39.1 Endpoint: 19.4 vs 18.3 vs 31.6 (p<0.0001 for both interventions vs placebo, no difference between treatment groups) CPRS-R at 11am Total Score (MTS vs MOS vs Placebo) Baseline: 52.6 vs 51.2 vs 49.6 Endpoint: 24.6 vs 28.4 vs 37.0 (p=0.0001 for MTS vs Placebo and p=0.0032 for MOS vs Placebo, no difference between treatment groups) CPRS-R at 3pm Total Score (MTS vs MOS vs Placebo) Baseline: 53.7 vs 51.4 vs 49.8 Endpoint: 24.1 vs 29.1 vs 37.7 (p=0.0001 for MTS vs Placebo and p=0.0288 for MOS vs Placebo, no difference between treatment groups)	Most frequently reported AEs (MTS vs MOS vs Placebo) Decreased appetite: 25 vs 17 vs 4 Insomnia: 13 vs 7 vs 4 Nausea: 12 vs 7 vs 2 Vomiting: 10 vs 9 vs 4 Weight decreased: 9 vs 7 vs 0 Tic: 7 vs 1 vs 0 Affect lability: 6 vs 3 vs 0 Nasal congestion: 6 vs 3 vs 1 Anorexia: 5 vs 3 vs 1 Nasopharyngitis: 5 vs 4 vs 2	113 withdrew total; 8 after randomization but prior to receiving medication; 27 in MTS group vs 25 in MOS group vs 53 in Placebo group Withdrawals due to AEs: MTS=7 vs MOS=2 vs Placebo=1	All authors have received grants or research money from multiple pharmaceutical companies	
Fitzpatrick 1992 (Poor)	SR vs SA vs Combination (SR+SA) p=NS for all All outcomes reported for Parent/Teacher Conners: 0.98/0.77 vs 0.96/0.73 vs 0.81/0.58 Inattention-Overactivity: 0.98/0.92 vs 1.01/0.87 vs 0.79/0.70 Noncompliance: 0.84/0.43 vs 0.80/0.48 vs 0.62/0.25 Aggression: 0.68/0.31 vs 0.56/0.24 vs 0.60/0.26 Hyperactivity: 0.22/-0.12 vs 0.20/-0.16 vs 0.18/-0.29 Attention: 0.72/0.88 vs 0.81/1.01 vs 0.91/1.05 Comments valence: -0.05/0.20 vs 0.17/0.19 vs 0.18/0.40 Other ratings: Parent ranks: 2.16 vs 2.18 vs 1.87 Laboratory rating: 0.13 vs 0.13 vs 0.09 Weight (kg): 31.59 vs 31.41 vs 31.33	Percentage of patients with side effects: SR vs SA vs Combination, p=NS for all Sleep problem: 36.8 vs 42.1 vs 63.2 Appetite decrease: 36.8 vs 15.8 vs 26.3 Crying: 21.0 vs 15.8 vs 26.3 Sadness: 0.0 vs 10.5 vs 0.0 Unhappiness: 21.0 vs 5.3 vs 15.8 Anger: 31.6 vs 10.5 vs 26.3 Headaches: 10.5 vs 10.5 vs 5.3 Increased thirst: 5.3 vs 0 vs 0 Dry mouth: 0 vs 0 vs 0 Nausea: 0 vs 5.3 vs 0 Stomachaches: 0 vs 5.3 vs 0 Shakiness: 0 vs 0 vs 5.3	NR NR	NIMH Grant MH38118, CIBA-GEIGY provided placebo tablets	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Garg 2014 India (Poor)	Children age 6 to 14 y with diagnosis of ADHD according to Diagnostic and Statistical Manual of Mental Disorder-IV-Text Revision and having moderate to severe illness as assessed by Clinical Global Impressions Severity Scale (CGI-S).	A: IR methylphenidate QD or bid for 8 weeks. Patients started on 5 mg QD. Effort made to increase dose up to 1 mg/kg/d QD or bid based on response and tolerability. B: Atomoxetine QD or bid. Patients started on 10 mg QD for 8 weeks. Effort made to increase dose up to 1.2 mg/kg/d QD or bid based on response and tolerability. Weekly increments of 5 mg were tried for both methylphenidate and atomoxetine	No ADHD medications in the previous month	Age (mean), y: 8.6 Gender, %: 18.8 female Ethnicity: NR	Type of ADHD, %: Inattention: 22 Hyperactive/impulsive: 8.6 Combined: 69.5	84	17/0/69

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Garg 2014 India (Poor)	IR Methylphenidate vs. Atomoxetine Treatment Response (mean difference from baseline to week 8 (SD), intragroup p-value) Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS) Total Score: -26.69 (1.99), p<0.001 vs. -29.32 (15.49), p<0.001; Intergroup p=0.500 Clinical Global Impression Severity Scale (CGI-S): -2.04 (1.15), p<0.001 vs. -2.04 (1.37), p<0.001; Intergroup p=0.997 Vanderbilt ADHD Diagnostic Teacher Rating Scale (VADPTS): -17.26 (10.12), p<0.001 vs. -14.10 (9.41), p<0.001; intergroup p=0.264 25% improvement from baseline (VADPRS): 90.7% vs. 86.2% 25% improvement from 3rd week on with mean dose: 11.59 mg/d vs. 14.03 mg/d Mean dose with maximum efficacy and tolerability at end of study: 17.35 mg/d vs. 17.46 mg/d	IR Methylphenidate vs. Atomoxetine 18 (55%) of methylphenidate and 20 (56%) of atomoxetine patients developed side effects. No significant difference between the two groups in the occurrence of various adverse effects. Specific adverse events Insomnia, no. (%): 1 (3.1) vs. 0	IR Methylphenidate vs. Atomoxetine Total withdrawals, no.: 6 vs. 11 Due to AE, no.: 3 vs. 3	None	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Gau 2006 Taiwan (Fair)	Patients, aged 6–15, with a clinical diagnosis of any subtype of ADHD. Patients were included in this study if they were taking MPH on a total daily dose of MPH of 10 mg but not more than 40 mg for past 3 months. They were able to comply with the study visit schedules; and their mothers and teachers were willing and able to complete the weekly assessments.	OROS MPH Mean Dose: 27.7 mg Dose Range: 18-36 mg IR MPH Mean Dose: 26.7 mg Dose Range: 15-30 mg	NR	Mean age=10.5 yrs (Range=6-15 yrs) 90.6% male Ethnicity: NR (study completed in Taiwan)	ADHD diagnosis: Combined: 78.1% Inattentive: 18.8% Hyperactive: 3.1% CTRS-R:S, mean (SD): 72.6 (11.5) CPRS-R:s, mean (SD): 77.6 (9.7) SKAMP, mean (SD): 72.5 (15.5) SAICA, mean (SD): 62.6 (12.5) BSEQ, mean (SD): 24.1 (20.6) Vital signs, mean (SD): Systolic pressure : 97.2 (15.3) Diastolic pressure: 58.2 (10.9) Heart rate: 84.9 (14.8)	64	0/0/64

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Gau 2006 Taiwan (Fair)	OROS vs IR **CTRS-R, Short Form-C, mean (SD):** Day 13-Baseline: Inattention: -1.38 (2.30) vs. -0.84 (1.97) Hyperactivity-Impulsivity: -3.16 (3.76) vs. -3.22 (4.09) Oppositional: -2.13 (2.97) vs. -1.58 (3.55) ADHD-index: -5.58 (6.38) vs. -5.97 (6.59) Day 27-Baseline, mean (SD) OROS vs IR: Inattention: -1.90 (3.00) vs. -1.44 (2.12) Hyperactivity-Impulsivity: -4.94 (4.11) vs. -4.00 (5.13) Oppositional: -3.03 (3.93) vs. -1.91 (3.90) ADHD-index: -9.20 (7.36) vs. -7.13 (7.62) **CPRS-R, Short Form-C, mean (SD):** Day 13-Baseline: Inattention: -4.78 (5.28) vs. -4.72 (5.31) Hyperactivity-Impulsivity: -6.22 (5.13) vs. -5.25 (5.06) Oppositional: -3.69 (3.36) vs. -3.56 (3.53) ADHD-index: -9.97 (8.26) vs. -9.66 (8.23) Day 27-Baseline: Inattention: -5.63 (5.14) vs. -4.19 (4.84) Hyperactivity-Impulsivity: -7.53 (4.84) vs. -5.84 (5.01) Oppositional: -3.87 (3.32) vs. -3.41 (3.79) ADHD-index: -11.59 (7.82) vs. -9.03 (8.29) **SKAMP, mean (SD):** Day 13-Baseline: Attention: -1.77 (3.16) vs. -1.72 (4.08) Deportment: -2.77 (4.05) vs. -3.25 (4.13) Day 27-Baseline: Attention: -3.71 (3.39) vs. -2.98 (5.29) Deportment: -4.65 (5.53) vs. -4.41 (6.71) At final assessment, OROS group had greater proportion of subjects being very much or much improved than the IR MPH group in CGI rating (84.4% vs. 56.3%, p=0.014)	Percentage of side effects with increased BSEQ score from baseline, day 27, OROS vs. IR MPH: Decreased appetite: 46.9 vs. 59.4 (p=0.316) Insomnia/sleep trouble: 40.6 vs. 46.9 (p=0.614) Stomachache: 31.3 vs. 25.0 (p=0.578) Headache: 21.9 vs. 34.4 (p=0.266) Nightmares: 7.8 vs. 25.0 (0.351) Uninterested in others: 28.1 vs. 40.6 (p=0.292) Irritable: 9.4 vs. 21.9 (p=0.169) Dry mouth: 31.3 vs. 17.2 (p=0.79) Sad/unhappy, prone to crying: 31.3 vs. 43.8 (p=0.302) Anxious: 18.7 vs. 31.3 (p=0.248) Bites fingernails: 18.7 vs. 25.0 (p=0.545) Drowsiness: 7.8 vs. 18.8 (p=0.741) Tics or nervous movements: 7.8 vs. 18.8 (p=0.741) No difference in vital signs on day 28 between groups	0/0	Jansessen-Cilag, Taiwan.	

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Gross 1976 (Poor)	Diagnosis of having Minimal Brain Dysfunction or Hyperkinetic Syndrome, based largely on the criteria of Clements and Peters, and showing a majority of the following traits: restlessness, hyperactivity or excessive daydreaming, short attention span, distractibility, labile emotionality or temper tantrums, overreaction to stimuli, lack of appropriate cautiousness or fear	Age group 3-4/5-6/7-8/9-11/12-14: Dextroamphetamine: 2.5/4.5/7.25/10/11.25 mg Methylphenidate: 4.5/10/15/20/22.5 mg 1 week, then crossover AM and noon	NR	NR NR NR	NR	50	2 (4%) withdrawn/lost to fu NR/analyzed: dextroamphetamine= 48 vs methylphenidate=46
Hervas 2013 11 European countries, US, Canada NCT01244490 (Good)	Patients aged 6–17 y with a diagnosis of ADHD of at least moderate severity, as defined by a baseline ADHD-RS-IV with a total score of 32 or higher and a minimum Clinical Global Impression-Severity (CGI-S) score of 4.	A. Guanfacine extended-release (GXR): optimal dose 0.05–0.12 mg/kg/day; children 6–12 y: 1–4 mg/day; adolescents 13–17 y: 1–7 mg/day B. Atomoxetine (ATX): 0.5–1.4 mg/kg/day in children and adolescents weighing < 70 kg at baseline; 40–100 mg/day in children and adolescents weighing 70 mg or more at baseline C. Placebo QD Drug dosage was titrated baseline to week 4 for dose-optimization every week, at the discretion of the physician. Duration of study: 10 weeks if 6–12 y and 13 weeks if 13–17 y.	NR	Age (mean), y: 10.8 Gender, % female: 26 Ethnicity: NR	GXR vs ATX vs Placebo ADHD subtype, %: Predominantly inattentive: 13.2 vs 8.9 vs 9.9 Predominantly hyperactive-impulsive: 5.3 vs 2.7 vs 4.5 Combined subtype: 81.6 vs 88.4 vs 85.6 Mean (SD) baseline ADHD-RS-IV score: 43.1 (5.47) vs 43.7 (5.86) vs 43.2 (5.60) Baseline CGI-S, %: Moderately ill: 18.4 vs 20.5 vs 29.7 Markedly ill: 52.6 vs 47.3 vs 44.1 Severely ill: 26.3 vs 29.5 vs 24.3 Extremely ill: 2.6 vs 2.7 vs 1.8 Current psychiatric comorbidities, %: None: 85.1 vs 90.2 vs 86.5 Diagnosis of ODD: 14.9 vs 8.9 vs 12.6 Other: 0.9 vs 0.9 vs 0.9 Oppositional symptoms, %: 53.1 vs 61.8 vs 54.1	338	66/9/337

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Gross 1976 (Poor)	Average improvement: 2.3 vs 2.2; p=NS	Average improvement in average side effects: 0.4 vs 0.5; p=NS	2 (4%) NR	NR	
Hervas 2013 11 European countries, US, Canada NCT01244490 (Good)	GXR vs ATX vs Placebo The LS mean (SD) change in ADHD-RS-IV total score from baseline to Visit 15: -23.9 (12.41) vs -18.6 (11.91) vs -15.0 (13.07) The LS mean (SD) change in ADHD-RS-IV total score from baseline to Visit 15 (by GXR weight-adjusted dose: 0.01-0.04 mg/kg, 0.05-0.08 mg/kg, 0.09-0.12 mg/kg, 0.13-0.16 mg/kg): -23.1 (15.99) vs -22.3 (12.03) vs -26.2 (11.24) vs -21.2 (13.90) % of patients 'very much improved' or 'much improved' in CGI-I at visit 15: 67.9 vs 56.3 vs 44.1 Difference in LS mean change from baseline in ADHD-RS-IV total score at Visit 15 (GXR vs ATX): -5.1 (95% CI, -8.2, -2.0, p=0.001; effect size, 0.440)* *secondary analysis, not controlled for multiplicity	GXR vs ATX vs Placebo, % Any TEAE: 77.2 vs 67.9 vs 65.8 Discontinuation from the study due to TEAE: 7.9 vs 4.5 vs 0.9 Insomnia: 11.4 vs 7.1 vs 6.3 Decreased appetite: 13.2 vs 27.7 vs 10.8 Anxiety: 7.9 vs 6.3 vs 7.2 Abuse potential, tics, and sexual dysfunction: NR	GXR vs ATX vs Placebo, n (%) Total withdrawals: 24 (20.9) vs 23 (20.5) vs 19 (17.1) Due to TEAE/Adverse Event: 9 (7.8) vs 5 (4.5) vs 1 (0.9)	Shire Development, LLC	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
James 2001 US (Poor)	DSM-IV criteria for combined-type ADHD; ADHD symptoms present in at least two settings	Adderall Dextroamphetamine, immediate release Dextroamphetamine spansules Placebo 2 weeks each Dosages were based on age, weight, prior medication experience, and symptom severity. Overall mean low dose was 7.8 mg and mean high dose was 12.8 mg. Dose order was randomized across subjects, but the same order, either increasing (n=18) or decreasing (n=17) was used for a given subject. The last 11 subjects received equal doses of both immediate-release formulations, but received increased dextroamphetamine spansules by 5 mg to more closely approximate clinical use patterns.	NR	Mean age=9.1 60% male 18 (51.4%) White 9 (25.7%) African Americans 7 (20%) Latinos 1 (2.8%) Asian Americans	15 (42.8%) naïve to stimulant treatment WISC-III Verbal standard score=102.5 Performance standard score=96.6 Full scale standard score=99.8 CBCL Attention Problems T score=72.5 TRF Attention Problems T score=72.3	35	0/0/35
Kauffman 1981 (Fair)	Children diagnosed as "hyperactive," according to a set of predetermined clinical criteria	Dextroamphetamine 10-60 mg Methylphenidate 5-30 mg Placebo Twice daily: morning and noon 6 weeks, then crossover	NR	Mean age NR 100% male 100% white	NR	12	NR/NR/12

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
James 2001 US (Poor)	Adderall vs dextroamphetamine spansules vs immediate release dextroamphetamine vs placebo; differences are insignificant unless otherwise noted CTRS Hyperactivity T score obtained from 9 AM to 12:30 PM: 50.6 vs 53.7 vs 50.5 vs 63.1; DEX IR > DEX span, p<0.025 CPRS Hyperactivity factor score obtained between 1 PM and 3 PM: 2.8 vs 2.3 vs 2.5 vs 3.8; DEX span > ADL, p=0.04 CPS Hyperactivity T score obtained between 4 PM and 7 PM (only available for n=15): 58.6 vs 60.0 vs 60.5 vs 68.0; Dex span > placebo (p=0.007), ADL > placebo (p=0.03), DEX IR = placebo Total attempted math problems: 171.6 vs 187.0 vs 177.4; DEX IR > placebo (p=0.01), DEX span > placebo (p=0.003), ADL = placebo Total correct math problems: 164.6 vs 177.6 vs 167.6 vs 140.2; DEX IR > placebo (p=0.01), DEX span > placebo (p=0.003), ADL=placebo Sleep (hr): 7.6 vs 7.2 vs 7.4 vs 7.8; DEX span and DEX IR decreased sleep > placebo (p<0.001 and p=0.02), ADL=placebo	SERS N#: 3.3 vs 2.9 vs 2.6 vs 2.0 SERS-N sev: 2.7 vs 3.1 vs 2.7 vs 1.8 SERS-P#: 6.3 vs 6.7 vs 6.4 vs 5.9 SERS-P sev: 3.2 3.7 vs 3.2 vs 2.8 Weight (kg): 32.6 vs 32.5 vs 32.7 vs 33.3 Mean magnitude of adverse effects rated by parents (n=20); staff nurse (n=29) for Adderall, immediate-release dextroamphetamine, dextroamphetamine spansules and placebo, uncorrected p-values from ANOVA Trouble sleeping: 3.5 vs 3.0 vs 3.3 vs 2.5, p=0.55; nurses didn't rate Nightmares: 0.6 vs 0.6 vs 0.3 vs 0.3, p=0.24 Stomach aches: 1.0 vs 0.9 vs 1.1 vs 1.0, p=0.97; 0.5 vs 0.5 vs 0.8 vs 0.4, p=0.59 Headaches: 0.9 vs 0.8 vs 0.7 vs 1.0, p=0.89; 0.1 vs 0.2 vs 0.2 vs 0.1; p=0.41 Tics: 0.8 vs 1.2 vs 1.4 vs 0.9; p=0.16; 0.4 vs 0.3 vs 0.3 vs 0.2, p=0.34	0 withdrawals; 0 withdrawals due to adverse events	NR	
Kauffman 1981 (Fair)	% patients with positive urinalysis: 60 vs 67; p=NS % of patient-weeks with missed doses recorded: 18 vs 13; p=NS	Anorexia (incidence/patient-week): 0.32 vs 0.26; both significantly different from placebo Insomnia (incidence/patient-week): 0.20 vs 0.36; only methylphenidate significantly different from placebo Mean change in weight (kg): -0.86 vs +0.11; significant difference between active drugs (p NR) Mean change in height (cm): +0.4 vs +0.4; neither significantly different from placebo	NR NR	Ciba-Geigy Corp.	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Kemner 2005 FOCUS US (Poor)	Children 6 to 12 years of age; meet criteria for a primary diagnosis of ADHD (any subtype) according to the DSM-IV-TR; investigator-rated ADHD-RS score of at least 24 and a Clinical Global Impression-Severity of Illness scale (CGI-S) score of at least 4 ("moderately ill" or worse)	Mean dosages for weeks 1/2/3: Atomoxetine: 32.1 mg/36.8 mg/36.7 mg OROS MPH: 26.8 mg/32.7 mg/32.7 mg (Investigators were allowed to select starting doses and adjust dosages as deemed necessary) Duration: 3 weeks	NR	Mean age=8.9 years 74% male 76.74 white	ADHD subtype Combined: 72% Hyperactive-impulsive: 15% Inattentive: 13% ADHD RS-Investigator-scored (mean): 39.3	1323	NR/NR/NR

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kemner 2005 FOCUS US (Poor)	OROS MPH vs atomoxetine: ADHD RS Total score (mean change in points): -20.24 vs -16; mean difference=4.24 (p<0.001) ADHD-RS responder rates (% pts with 25% or greater reduction in ADHD-RS): 80.2% vs 68.7%; p<0.001 CGI-I responder rates (% pts with scores of 2 or lower): 68.6% vs 52.8%; p<0.001 PSQ mean reductions (points): -9.1 vs -8.7; p<0.001	OROS MPH vs atomoxetine (%) - NS unless otherwise noted: Overall AE incidence: 26.3% vs 28.3% Serious AEs (resulting in prolonged inpatient hospitalization, significant disability or incapacity, onset of life-threatening conditions: 0.8% vs 0.2% Abdominal pain: 0.4 vs 1.1 Abdominal pain, upper: 3.5 vs 4.2 Abnormal behavior: 1.4 vs 1.5 Aggression: 1.2 vs 0.6 Crying: 1.5 vs 0.4 Decreased appetite*: 5.8 vs 3.0 Dizziness: 0.8 vs 1.5 Emotional disturbance: 0.6 vs 1.1 Fatigue*: 0.4 vs 3.0 Headache: 3.9 vs 4.2 Initial insomnia: 1.1 vs 0.2 Insomnia: 6.2 vs 2.3 Irritability: 0.8 vs 1.5 Mood alteration: 1.2 vs 1.3 Nausea*: 1.1 vs 4.9 Somnolence*: 0.9 vs 4.2 Vomiting: 1.3 vs 2.1 *=difference noted in text, but p-value NR	Withdrawals due to adverse events: 4.8% vs 5.5%, p-value NR Overall withdrawals NR	McNeil Consumer and Specialty Pharmaceuticals	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Kratochvil 2002 US/Canada (Fair)	Boys aged 7 to 15 years and girls aged 7 to 9 years who met DSM-IV diagnostic criteria for ADHD. Diagnosis was confirmed by clinical interview and by structured interview with the Schedule for Affective Disorders and Schizophrenia for School-Age Children ADHD module. All patients had a severity score of at least 1.5 standard deviations above age and gender norms on the ADHD-IV Rating Scale-Parent Version: Investigator Administered (ADHD RS)	Atomoxetine CYP 2D6 extensive metabolizers: titrated to a maximum of 2 mg/kg per day and administered as a divided dose in the morning and late afternoon (mean=1.40 mg/kg per day) CYP 2D6 poor metabolizers: Initiated at 0.2 mg/kg per day and titrated to 1.0 mg/kg per day (mean=0.48 mg/kg per day) Methylphenidate: Beginning at 5 mg from one to three times daily with an ascending dose titration based on the investigators assessment of clinical response/tolerability; maximum dose of 60 mg (mean dose=0.85 mg/kg per day) 10 weeks	NR	Mean age=10.4 92.5% male 76.7% white	ADHD subtype Combined: 75.9% Hyperactive-impulsive: 1.3% Inattentive: 22.8% ADHD RS-Parent scored (mean): 76.7	228	85 (37.3%) withdrawn/5 (2.2%) lost to fu/218 analyzed (atomoxetine n=178; methylphenidate n=40)

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kratochvil 2002 US/Canada (Fair)	Atomoxetine vs methylphenidate (mean changes) (p=NS for all) ADHD RS Total score: -19.44 vs -17.78 ADHD RS Hyperactivity/Impulsivity: -9.50 vs -8.48 ADHD RS Inattention subscale: -9.94 vs -9.30 CGI-ADHD-Severity score: -1.67 vs -1.70 CPRS-R ADHD Index: -11.36 vs -11.97 CPRS-R Cognitive: -6.17 vs -5.69 CPRS-R Hyperactive: -5.56 vs -4.78 ADHD RS-Parent Total T score: -18.83 vs -18.38	Atomoxetine vs methylphenidate; p=NS unless otherwise noted Headache: 57 (31%) vs 13 (32.5%) Abdominal pain: 43 (23.4%) vs 7 (17.5%) Anorexia: 35 (19%) vs 6 (15%) Rhinitis: 33 (17.9%) vs 8 (20%) Nervousness: 29 (15.8%) vs 4 (10%) Vomiting: 22 (12%) vs 0, p=0.017 Fever: 20 (10.9%) vs 4 (10%) Somnolence: 20 (10.9%) vs 0, p=0.029 Nausea: 19 (10.3%) vs 2 (5%) Insomnia: 17 (9.2%) vs 7 (17.5%) Asthenia: 14 (7.6%) vs 1 (2.5%) Diarrhea: 13 (7.1%) vs 1 (2.5%) Emotional lability: 11 (6%) vs 2 (5%) Pharyngitis: 11 (6%) vs 3 (7.5%) Tachycardia: 11 (6%) vs 2 (5%) Accidental Injury: 10 (5.4%) vs 5 (12.5%) Cough increased: 10 (5.4%) vs 2 (5%) Dyspepsia: 10 (5.4%) vs 2 (5.0%) Pain: 10 (5.4%) vs 1 (2.5%) Flu syndrome: 9 (4.9%) vs 4 (10%) Infection: 8 (4.3%) vs 3 (7.5%) Rash: 7 (3.8%) vs 3 (7.5%) Depression: 5 (2.7%) vs 2 (5%) Weight loss: 5 (2.7%) vs 2 (5%) Hyperkinesia: 3 (1.6%) vs 2 (5%) Palpitation: 3 (1.6%) vs 2 (5%) Thinking abnormal: 0 vs 2 (5%); p=0.031	Total withdrawals: 66 (35.9%) vs 19 (43.2%); p=NS Withdrawals due to adverse events: 10 (5.4%) vs 5 (11.4%); p=NS	Eli Lilly	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Lopez 2003 (Fair)	Children who met ADHD criteria based on the Diagnostic Interview Schedule for Children	Methylphenidate osmotic controlled release delivery system (MPH OROS) 18 mg or 36 mg Methylphenidate spheroidal oral drug absorption system (MPH SODAS) 20 mg Placebo 5-single dose test sessions (one practice visit, three active treatments and placebo)	NR	Mean age=9.0 80.5% male 36% White 27% African American 36% Hispanic	NR	36	0 withdrawn/0 lost to fu/36 analyzed

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Lopez 2003 (Fair)	MPH SODAS 20mg vs MPH OROS 18mg vs MPH OROS 36mg vs Placebo; p=values reflect comparison to MPH SODAS Mean change from baseline for SKAMP-attention $AUC_{(0-4)}$: -2.48 vs -1.36 (p=0.015) vs -1.55 (p=0.043) vs 1.24 (p<0.001) $AUC_{(0-8)}$: -4.48 vs -2.72 (p=NS) vs -3.24 (p=NS) vs 3.79 (p<0.001) Greatest improvement: 54% at 2 hrs vs 35% at 1 hour vs 35% at 3 hrs Mean change from baseline for SKAMP-deportment $AUC_{(0-4)}$: -1.67 vs -0.28 (p<0.001) vs -0.55 (p=0.004) vs 0.95 (p<0.001) $AUC_{(0-8)}$: -2.81 vs -0.82 (p=0.018) vs -1.34 (p=0.078) vs 2.85 (p<0.001) Greatest improvement: 63%/2 hrs vs 32%/8 hrs vs 40%/6 hrs Mean change from baseline for SKAMP-combined $AUC_{(0-4)}$: -2.05 vs -0.78 (p<0.001) vs -1.01 (p=0.003) vs 1.09 (p<0.001) $AUC_{(0-8)}$: -3.58 vs -1.70 (p=0.01) vs -2.22 (p=0.061) vs 3.28 (p<0.001) Math test-attempted $AUC_{(0-4)}$: 112 vs 62 (p=0.066) vs 69 (p=NS) vs -39 (p<0.001) $AUC_{(0-8)}$: 202 vs 115 (p=NS) vs 137 (p=NS) vs -123 (p<0.001) Greatest improvement: 52%/2 hrs/41% at 1 hr; 26%/8 hrs Math Test Correct $AUC_{(0-4)}$: 104.07 vs 45.44 (p=0.026) vs 58.55 (p=0.080) vs -40.6 (p<0.001) $AUC_{(0-8)}$: 183 vs 100 (p=NS) vs 117 (p=NS) vs -124.7 (p<0.001) Greatest improvement: 52%/2 hrs vs 39%/1 hr vs 26%/8 hrs	Number (proportion) patients with at least one adverse event: 1 (2.7%) vs 1 (2.7%) vs 1 (2.7%)	Total withdrawals=0 Withdrawals due to adverse events=0	Novartis Pharmaceuticals	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Manos 1999 (Poor)	DSM-IV criteria for ADHD; presence of at least 6 symptoms of inattention and/or at least 6 symptoms of hyperactivity/impulsivity; symptoms significantly interfered with functioning at home and at school as noted during structured (Computerized Diagnostic Interview Schedule for Children) or semistructured clinical interviews; symptom severity on broad-band (Conners ASQ) and narrow-band (ARS) rating scales was at threshold or above (i.e., rated 2 or 3); multiple raters agreed to the presence of the symptoms; empirical comparison to norms indicated at least a 1.5 SD cutoff on at least one rating scale	Adderall (once daily) vs methylphenidate (twice daily) 1-week for each condition Fixed dosage: 4 conditions: (1) placebo; (2) 5 mg; (3) 10 mg; (4) 15 mg Six dose orders were used such that the highest dose (15 mg) was given only when preceded by the moderate dose (10 mg) Dose orders were assigned in a random fashion Parents blind to dosage	NR	Mean age=10.1 78.6% male 92.8% white	Inattentive type=45.2% Combined type=54.8% Mood disorder=1.2% Anxiety disorder=4.8% Learning disability=47.6%	159	MPH n=42 (matched by "hand-selecting" by age, diagnostic category and gender to Adderall group), Adderall n=42

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Manos 1999 (Poor)	"Best dose" comparisons of Adderall vs methylphenidate Parent ratings (no significant differences, but p-values NR) ASQ: 49.83 vs 50.64 ARS: 11.79 vs 10.10 Composite ratings: 3.50 vs 3.31 Teacher ratings (no significant differences, but p-values NR) ASQ: 51.47 vs 56.12 SSQ-R, total: 1.67 vs 1.92 SSQ-R, part: 2.23 vs 2.68	Results described as "no differences", but p-values NR Insomnia: 5 (11.9%) vs 2 (4.8%) Decreased appetite: 0 vs 1(2.4%) Tics/nervousness: 0 vs 0	NR NR	NIDA, Maternal and Child Health Program	

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Matochik 1994 US (Fair)	Subjects had to be adults who met following: 1) DSM-II criteria for ADHD 2) Utah criteria for attention deficit disorder in adulthood 3) a childhood history of ADHD 4) no history of an other major psychiatric disorders.	DAMP 5 mg/day, up to 5-15 mg/day OR methylphenidate 5 mg/day, up to 5-25 mg/day. Duration: 6-15 weeks	NR	mean age 35.5 y 21 males, 16 females Ethnicity NR	**Characteristic: methylphenidate vs d-amphetamine** had parents with attention-deficit disorder, residual type: 11/19 vs 12/18 had children with ADHD: 10/19 vs 10/18 WAIS IQ mean score: 108 vs 107 Wide Range Achievement Test scores Reading: 106.1 vs 102.7 Spelling: 105.6 vs 101.9 Arithmetic: 100.1 vs 97.2 Years of education: 15.4 vs 15.5 Socioeconomic status: 61.2 vs 56.6	37	NR/NR/ 37 analyzed: methylphenidate: n=19 DAMP: n=18

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Matochik 1994 US (Fair)	**Behavioral Effects of methylphenidate vs d-amphetamine** measure; Mean score at end of drug treatment (methylphenidate); p-Value vs d-amphetamine; p-Value Conner's rating scale Self: 5.0; 0.0001 vs 4.6; 0.0001 Spouse/Other: 5.7; 0.0001 vs 8.3; 0.0001 "How I Feel" Questionnaire Feel cranky or tired: 0.5; 0.02 vs NR; NR Have trouble keeping my mind on things: 0.5; 0.0001 vs 0.6; 0.0001 Feel like something bad might happen: 0.1; 0.008 vs NR; NR Feel restless, like moving around: 0.8; 0.0002 vs NR; NR Feel things may get messed up today: 0.0; NR vs NR; NR Feel I'm not much good at things: 0.3; 0.007 vs 0.2; 0.05 Feel sad: NR; NR vs 2.2; 0.008 Feel like I don't want to play with anyone: NR; NR vs 0.1; 0.01 Feel in a good mood: NR; NR vs 2.2; 0.008 Feel like my thoughts are going fast: NR; NR vs 0.2; 0.05 Feel tired and slow: NR; NR vs 0.0; NR Subject's Treatment Emergent Symptom Scale Trouble with sitting still: 0.7; 0.0001 vs 0.7; 0.002 Feeling sleepy: 0.4; 0.007 vs 0.2; 0.05 Not being happy: 0.3; 0.02 vs NR; NR Trouble with paying attention: 0.4; 0.0001 vs 0.6; 0.0001 Colds or sniffles: NR; NR vs 0.1; 0.01 Headaches: NR; NR vs 0.2; 0.03 Tiredness: NR; NR vs 0.3; 0.03 Trouble getting or staying asleep: NR; NR vs 0.3; 0.04 Getting along with parents: NR; NR vs 04; 0.007 Crying: NR; NR vs 0.1; 0.04 Being sad: NR; NR vs 0.1; 0.04	1 subject reported adverse events (not specified) within first 2 weeks, and was immediately switched to other drug	None	NR	

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McCracken 2003 US (Fair)	Potential subjects were screened to meet the following eligibility criteria: age 6 to 12 years; diagnosis of DSM-IV ADHD (combined or hyperactive-impulsive subtype as determined by a comprehensive clinician evaluation and selected modules of the Diagnostic Interview Schedule for Children, Version IV-Lifetime [DISC-IV]) administered by a research staff member with suitable training; no evidence of mental retardation; and history of positive response to psychostimulant medication, or no prior stimulant treatment. Information pertaining to co-occurring psychopathology from the clinical evaluation was supplemented by the Comorbid Disorders Checklist, a parent-report questionnaire composed of DSM-III-R symptom items. All diagnoses were based on DSM-IV criteria.	SLI381 (Adderall XR) 10, 20, or 30mg, placebo, or active control (Adderall 10mg) Mean Dose: NR Subjects who tolerated initial exposure to SLI381 were randomly assigned in crossover design to each of five treatment weeks: SLI381 10mg, SLI381 20mg, SLI381 30mg, Adderall 10mg, and placebo, each administered daily at 7:30 AM	NR	Mean age= 9.5 yrs (SD 1.9) 86.3% male 49% white 15.7% black 23.5% Hispanic 5.9% Asian/Pacific Islander 5.9% other	ADHD diagnosis: Hyperactive-impulsive=2% Combined=98% Duration of prior stimulant treatment: mean=1.7 yrs (SD 1.7) ADHD treatment before study entry: amphetamine only=33.3% methylphenidate only=58.8% none listed=7.8%	51	2 of 51 withdrawn because of withdrawal of consent; 49 randomized for crossover treatment 2 of 47 withdrawn (1 stomachache, 1 developed an exclusion criterion) 45 completed 5 weeks of double-blind portion of study (all treatment conditions) 3 withdrew in extra or "makeup" week ITT=49

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McCracken 2003 US (Fair)	**p-values for active drug vs placebo:** **Adderall XR 30mg/20mg/10mg/Adderall 10mg** **SKAMP Attention (hours post-dose)** 1.5-hr: 0.0015/0.0513/0.5846/0.0025 4.5-hr: <0.0001/0.0023/0.0269/0.0005 6.0-hr: <0.0001/<0.0001/0.0003/0.0005 7.5-hr: <0.0001/<0.0001/0.0001/0.0002 9.0-hr: 0.0001/0.0072/0.2442/0.8264 10.5-hr: <0.0001/<0.0001/0.0062/0.3250 12.0-hr: 0.0034/0.0077/0.0626/0.3064 **SKAMP Deportment (hours post-dose)** 1.5-hr: 0.0002/0.0031/0.0725/<0.0001 4.5-hr: <0.0001/<0.0001/0.0090/<0.0001 6.0-hr: <0.0001/<0.0001/<0.0001/<0.0001 7.5-hr: <0.0001/<0.0001/0.0083/0.0004 10.5-hr: <0.0001/0.0021/0.0724/0.0246 12.0-hr: 0.0062/0.0531/0.9878/0.7901 **PERMP no. attempted (hours post-dose)** 1.5-hr: 0.0030/0.0283/0.0920/0.0004 4.5-hr: <0.0001/0.0006/0.0136/0.0850 6.0-hr: <0.0001/<0.0001/0.0001/0.0015 7.5-hr: <0.0001/<0.0001/0.0017/0.0157 9.0-hr: <0.0001/0.0001/0.0230/0.0048 10.5-hr: <0.0001/<0.0001/0.0101/0.7626/ 12.0-hr: 0.0017/0.0053/0.9938/0.7508 **PERMP no. correct (hours post-dose)** 1.5-hr: 0.0059/0.0333/0.1121/0.0007 4.5-hr: <0.0001/<0.0001/0.0020/0.0353 6.0-hr: <0.0001/<0.0001/<0.0001/0.0007 7.5-hr: <0.0001/<0.0001/0.0029/0.0667 9.0-hr: <0.0001/<0.0001/0.0128/0.0195 10.5-hr: <0.0001/<0.0001/0.0025/0.3424 12.0-hr: 0.0001/0.0007/0.5420/0.9304	Study medications well tolerated overall. No serious side effects reported or observed. Only anorexia displayed a dose-dependent pattern of increases for Adderall XR doses. Placebo (n=49) vs. Adderall 10mg (n=48) vs. SLI381 10mg(n=48) vs. SLI381 20mg (n=50) vs. SLI381 30mg (n=49) Nervousness: 29 (59.2%) vs. 22 (45.8%), 26 (54.2%) vs. 28 (56.0%) vs. 21 (42.9%) Insomnia: 10 (20.4%) vs. 17 (35.4%) vs. 6 (12.5%) vs. 16 (32.0%) vs. 14 (28.6%) Anxiety: 10 (20.4%) vs. 11 (22.9%) vs. 13 (27.1%) vs. 11 (22%) vs. 9 (18.4%) Emotional lability: 5 (10.2%) vs. 10 (20.8%) vs. 13 (27.1%) vs. 9 (18%) vs. 6 (12.2%) Depression: 5 (10.2%) vs. 4 (8.3%) vs. 5 (10.4%) vs 11 (22.0%) vs. 3 (6.1%) Abdominal pain: 12 (24.5%) vs. 16 (33.3%) vs. 14 (29.2%) vs 18 (36.0%) vs. 17 (34.7%) Headache: 12 (24.5%) vs. 12 (25.0%) vs. 12 (25.0%) vs. 15 (30.0%) vs. 12 (24.5%) Anorexia: 11 (22.4%) vs. 22 (45.8%) vs. 13 (27.1%) vs. 20 (40.0%) vs. 27 (55.1%)	Of the 49 randomized subjects, 3 withdrew due to AE's	Supported by a grant from Shire Pharmaceutical Development Inc.	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Mikami 2009 US	White adolescents ages 16 to 19 with a primary diagnosis of ADHD, who surpassed clinical cutoffs for ADHD on the ADHD Rating Scale IV and whose parent interview on the Diagnostic Interview Schedule for Children and independent adolescent interview on the Standardized Interview for Adult ADHD supported a diagnosis of ADHD.	A: OROS MPH 72 mg/d B: se-AMPH ER 30 mg/d Dosing schedule: Crossover study, 17 days for each phase (5 days titration period and 12 days on full dose) separated by a 2-week period when participants resumed limited routine medication regimen they were following before the start of the study. On day 10 or 17 of each treatment, patients were given placebo	NR (except during the washout period, where participants resumed regimen they were following before the study, usually methylphenidate or amphetamine on an as-needed or irregular basis, or no treatment)	Age: 17.8 years (SD 1.7) Male: 54% White: 100%	ADHD subtype: Combined: 60% Inattentive: 34% Hyperactive: 6% Medication prior to study: No medication: 5.7% Methylphenidate formulations: 60% Amphetamine formulations: 34.3%	35	NR/NR/35

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Mikami 2009 US	se-AMPH ER vs OROS MPH **Conners-adolescent report, mean (SD):** males: 0.13 (1.03) vs -0.15 (0.87); females: -0.42 (0.81) vs -0.72 (0.67); sex: F(1,32) = 3.98 (p<0.05); medication: F(2,31) = 23.08 (p<0.01); sex x medication: F(2,31) = 0.01; effect size sex x med: η^2 = .00 **HHC-adolescent report, mean (SD):** males: -0.17 (1.06) vs 0.07 (1.27); females: 0.15 (0.88) vs 0.00 (0.74); sex: F(1,30) = 0.05; medication: F(1,30) = 1.96; sex x medication: F(1,30) = 1.83; effect size sex x med: η2 = .05 **HHC-parent report, mean (SD):** males: 0.04 (1.02) vs 0.04 (1.07); females: -0.18 (0.97) vs 0.09 (1.10); sex: F(1,30) = 0.14; medication: F(1,30) = 0.05; sex x medication: F(1,30) = 0.97; effect size sex x med: η2 = .03 **Impaired driving score, mean (SD):** males: 0.07 (3.13) vs -0.69 (1.78); females: 0.24 (2.38) vs -1.48 (1.56); sex: F(1,33) = 0.43; medication: F(2,32) = 5.35 (p<0.01); sex x medication: F(2,32) = 0.28; effect size sex x med: η2 = .01	se-AMPH ER vs OROS MPH **Side effects scale, mean (SD):** males: -0.90 (0.97) vs -0.25 (0.81); females: 0.15 (1.20) vs -0.32 (1.02); sex: F(1,29) = 0.00; medication: F(2,29) = 5.17 (p<0.01); sex x medication: F(2,29) = 1.40; effect size sex x med: η2 = .04	NR	McNeil Consumer and Specialty Pharmaceuticals	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Muniz 2008 US (Fair)	Patients were 6-12 years with ADHD according to the DSM-IV-TR, who had been stabilized on a total daily dose or the nearest equivalent dose of 40 to 60 mg of *d,l*-MPH or 20 to 30 mg *d*-MPH for at least 2 weeks prior to screening. Children were excluded if they had a tic disorder or Tourette's syndrome, history of seizures, psychiatric illness or substance abuse disorder, taking prohibited concomitant medications or ADHD medication other than methylphenidate, taking antidepressant or psychotropic medications, had begun psychotherapy within 3 months prior to randomization or who were home schooled.	*d*-MPH-ER 20-30mg/day *d,l*-MPH-ER 36-54mg/day Placebo	NR	Mean age: 9.5 years 65.5% male 42.9% Caucasian 27.4% Black 28.6% Hispanic 1.2% other	DSM-IV ADHD diagnosis Inattentive type: 9 (10.7%) Combined type: 75 (89.3%)	84	3 withdrew 0 lost to fu 84 analyzed
Muniz 2008 US (Fair) Continued.							

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Muniz 2008 US (Fair)	d-MPH 20mg/day vs d,l-MPH 36mg/day; d-MPH 30mg/day vs d,l-MPH 54mg/day SKAMP-Combined score change from pre-dose to 2-hours post-dose -10.65 vs -5.94 (p<0.001); -11.17 vs -7.52 (p=0.001) d-MPH 20mg vs Placebo: p<0.05; d-MPH 30mg vs Placebo: p<0.001 d,l-MPH 36mg and d,l-MPH 54 mg vs Placebo: p<0.001 SKAMP-Attention score change from pre-dose d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.001 at 1 and 3 hours; p<0.05 at 2 and 6 hours d,l-MPH 36 mg/day vs d-MPH 20mg/day: p<0.05 at 10 hours; p<0.001 at 11 and 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p<0.001at 1 and 3 hours; p<0.05 at 2, 4, and 6 hours d,l-MPH 54mg/day vs d-MPH 30mg/day: p<0.05 at 11 and 12 hours SKAMP-Deportment score change from pre-dose d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.001 at 1, 2, 3, and 4 hours d,l-MPH 36mg/day vs d-MPH 20mg/day: p<0.1 at 10, 11 and 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p=0.019 at 0.5 hours; p<0.001 at 1 and 2 hours; p<0.05 at 3 and 4 hours d,l-MPH 54mg/day vs d-MPH 30mg/day: p<0.05 at 11 and 12 hours	*d*-MPH 20mg/day vs *d*-MPH 30mg/day vs *d,l*- MPH 54mg/day vs *d,l*-MPH 36mg/day vs Placebo Total: 8 vs 15 vs 5 vs 12 vs 3 Headache: 4 vs 6 vs 2 vs 5 vs 0 Nausea: 1 vs 1 vs 1 vs 0 vs 0 Nasal congestion: 1 vs 1 vs 0 vs 1 vs 0 Decreased appetite: 0 vs 1 vs 1 vs 1 vs 0 Vomiting: 0 vs 1 vs 1 vs 0 vs 0 Skin laceration: 0 vs 1 vs 0 vs 1 vs 0 Somnolence: 1 vs 1 vs 0 vs 0 vs 0 Insomnia: 0 vs 1 vs 0 vs 1 vs 0 Abdominal pain upper: 1 vs 1 vs 0 vs 0 vs 0 Abdominal pain: 0 vs 1 vs 0 vs 1 vs 0	3 withdrew consent, none withdrew due to AEs	All authors have received grants or research money from multiple pharmaceutical companies	
Muniz 2008 US (Fair) Continued.	Change in number of attempted math problems d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.05 at 1 and 3 hours d,l-MPH 36mg/day vs d-MPH 20mg/day: p=0.01 at 11 hours; p=0.001 at 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p<0.05 at 1, 3, and 4 hours Change in number of accurate math problems d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.05 at 1, 2, and 3 hours d,l-MPH 36mg/day vs d-MPH 20mg/day: p<0.05 at 11 and 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p<0.05 at 1, 2, 3, and 4 hours d,l-MPH 54mg/day vs d-MPH 30mg/day: p<0.05 at 11 and 12 hours				

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Newcorn 2008 US (Good/Fair)	Patients aged 6-16 years, who met DSM-IV criteria for ADHD, any subtype, symptom severity was ≥1.5 SD above the US age and gender norms as assessed by the ADHD-RS-IV - Parent version. Patients were excluded if they had seizures, bipolar disorder, a psychotic illness, or a pervasive development disorder or who were taking concomitant psychoactive medications; and those with anxiety and tic disorders.	Atomoxetine 0.8-1.8 mg/kg per day (administered as divided twice-daily dose) - mean final dose was 1.45 mg/kg per day or 53mg/day Osmotically released methylphenidate 18-54 mg/day (administered as a single morning dose) - mean final dose was 39.9 mg/day or 1.16 mg/kg per day for patients <12 years and 41.7 mg/day or 0.88 mg/kg per day for patients ≥12 years Placebo	NR	Mean age: Atomoxetine=10.3 years; Methylphenidate= 10.2; Placebo=10.1 74.2% male Ethnicity: NR	ADHD Subtype Hyperactive/impulsive: 2% Inattentive: 28% Combined: 70%	516	93 withdrew from acute phase; 42 withdrew from crossover phase 16 lost to follow up from acute phase; no lost to follow up in crossover phase 516 analyzed in acute phase; 178 analyzed in crossover phase

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Newcorn 2008 US (Good/Fair)	Atomoxetine vs MPH vs placebo (mean change) ADHD-RS total score: -14.4 vs -16.9 vs -7.3 (p=0.003 for Atomoxetine vs Placebo; p<0.001 for MPH vs Placebo; p=0.02 for Atomoxetine vs MPH) ADHD-RS total score for prior stimulant users: -12.4 vs -15.1 vs -6.2 (p=0.02 for MPH vs placebo; p=0.03 for MPH vs atomoxetine) ADHD-RS total score for those naïve to stimulants: -17.9 vs -19.7 vs -9.0 (p=0.004 for atomoxetine vs placebo; p<0.001 for MPH vs placebo) ADHD-RS inattentive subscale: -7.3 vs -9.0 vs -4.1 (p=0.006 for MPH vs atomoxetine) ADHD-RS inattentive subscale for prior stimulant users: -5.9 vs -7.8 vs -3.3 (p=0.02 for MPH vs atomoxetine) ADHD-RS inattentive subscale for those naive to stimulants: -9.7 vs -11.0 vs -5.2 ADHD-RS impulsivity/hyperactivity subscale: -7.1 vs -7.9 vs -3.2 ADHD-RS impulsivity/hyperactivity subscale for prior stimulant users: -6.5 vs -7.3 vs -2.8 ADHD-RS impulsivity/hyperactivity subscale for those naive to stimulants: -8.2 vs -8.7 vs -3.8 CGI ADHD severity index: -1.2 vs -1.5 vs -0.7 CGI ADHD severity index for prior stimulant users: -0.9 vs -1.3 vs -0.6 CGI ADHD severity index for those naive to stimulants: -1.5 vs -1.8 vs -0.8 CPRS ADHD Index: -7.8 vs -10.2 vs -2.3 CPRSADHD Index for prior stimulant users: -5.9 vs -8.2 vs -1.1 CPRS ADHD Index for those naive to stimulants: -10.9 vs -13.5 vs -3.9 Daily Parent Ratings of Evening and Morning Behavior - Revised; Morning: -0.31 vs -0.25 vs 0.61	Atomoxetine vs methylphenidate vs placebo Any: 149 (67%) vs 146 (67%) vs 40 (54%) Headache: 39 (18%) vs 25 (11%) vs 7 (10%) Decreased appetite: 31 (14%) vs 37 (17%) vs 2 (3%) Pain in upper abdomen: 24 (11%) vs 22 (10%) vs 4 (5%) Any report of insomnia: 15 (7%) vs 29 (13%) vs 1 (1%) Irritability: 14 (6%) vs 13 (6%) vs 1 (1%) Nausea: 9 (4%) vs 13 (6%) vs 6 (8%) Insomnia: 9 (4%) vs 17 (8%) vs 1 (1%) Vomiting not otherwise specified: 15 (7%) vs 8 (4%) vs 4 (5%) Somnolence: 14 (6%) vs 4 (2%) vs 3 (4%) Cough: 7 (3%) vs 8 (4%) vs 4 (5%) Fatigue: 12 (5%) vs 5 (2%) vs 1 (1%) Initial insomnia: 6 (3%) vs 12 (6%) vs 0 (0%)	93 withdrew from acute phase; 12 for AEs 42 withdrew from crossover phase; 3 for AEs	Eli Lilly	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Newcorn 2008 US (Good/Fair) Continued.							

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Newcorn 2008 US (Good/Fair) Continued.	Daily Parent Ratings of Evening and Morning Behavior - Revised; Evening: -0.48 vs -0.53 vs 0.60 CHQ psychosocial summary score: 11.9 vs 12.7 vs 12.0 CHQ psychosocial summary score for prior stimulant users: 11.4 vs 13.1 vs 12.1 CHQ psychosocial summary score for those naive to stimulants: 9.9 vs 9.8 vs 12.0 After Crossover: Response to either treatment arm 60 of 178 (34%) responded to either atomoxetine or MPH, but not both 78 of 178 (44%) responded to both treatments 40 of 178 (22%) did not respond to either treatment Of 70 patients who did not respond to MPH in the acute phase, 30 (43%) subsequently responded to atomoxetine Of 69 patients who did not respond to atomoxetine in the crossover phase, 29 (42%) had previously responded to MPH				

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Palumbo 2008/Daviss 2008 US (Fair)	Children ages 7 to 12 years of any race and ethnic background who were in school, and met DSM-IV criteria for ADHD of any subtype.	A: Clonidine (mean end-of-study dose 0.24±0.11 mg/d) B: Methylphenidate (mean end-of-study dose 30.2±18.9 mg/d) C: Combination: Clonidine (0.23±0.13 mg/d) + Methylphenidate (25.4±18.2 mg/d) D: Placebo (not reported on in this evidence table) for 16 weeks -- an 8-week dose titration period (4 weeks for clonidine, then 4 weeks for methylphenidate) and an 8-week maintenance dose period.	NR	Age: 9.5 years (SD 1.6) Male: 80.3% White: 77.9% Black: 10.7% Hispanic: 6.6% Other: 4.9%	Pubertal: 6.5% Family history: ADHD: 37.7% Tics: 4.1% Treatment history: Stimulant: 46.7% Clonidine: 6.6% Comorbid ODD: 47.1% Comorbid conduct disorder: 9.2%	122	44/6/NR

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Palumbo 2008/Daviss 2008 US (Fair)	Clonidine vs Methylphenidate vs Combination Conners ASQ-Teacher, mean (SD) changes from baseline to week 16: -3.35 (5.78) vs -5.07 (6.79) vs -7.28 (7.91) Treatment Effects on the Conners ASQ-Teacher: Methylphenidate vs. no methylphenidate: -2.9; 95% CI, -5.1 to -0.8; P=0.008 Clonidine vs. no clonidine: -1.4; 95% CI, -3.6 to 0.7; P=0.19 Methylphenidate x Clonidine interaction: P=0.69 Methylphenidate vs Clonidine: -1.5; 95% CI, -4.6 to 1.6; P=0.34 Combination vs Methylphenidate: -1.9; 95% CI, -4.9 to 1.2; P=0.23 Combination vs Clonidine: -3.4; 95% CI, -6.4 to -0.4; P=0.03 Treatment Effects on the Conners ASQ-Parent: Methylphenidate vs. no methylphenidate: -1.2; 95% CI, -3.7 to 1.2; P=0.31 Clonidine vs. no clonidine: -3.7; 95% CI, -6.1 to -1.3; P=0.003 Methylphenidate x Clonidine interaction: P=0.56 Methylphenidate vs Clonidine: 2.5; 95% CI, -1.0 to 5.9; P=0.16 Combination vs Methylphenidate: -3.0; 95% CI, -6.4 to 0.4; P=0.08	Methylphenidate vs Clonidine vs Combination One subject receiving combination therapy (0.2 mg/d of clonidine and 5 mg/d of methylphenidate) was withdrawn at week 14 after experiencing a prolonged QTc interval (>440 ms) as well as ECG findings suggestive of left ventricular hypertrophy. This child had a normal echocardiogram and never reported physical complaints suggestive of cardiovascular problems. A second subject taking methylphenidate 20 mg/d was withdrawn in the last week of the double-blind phase complaining of repeated incidences of tachycardia and heart palpitations. No abnormalities were observed in this subject's vital signs or ECGs. Severe AEs: 10 events (3 subjects) vs 30 events (10 subjects) vs 39 events (9 subjects) Weight, mean change (SD) in kg: 0.3 (2.3) vs 2.0 (2.9) vs 0.6 (2.3); taking Methylphenidate P=0.0007 Abnormal ECG rate, QTc >120 ms: 3.5% vs 6.5% vs 0.0% **AEs rated at least moderate on AEs log (occurring ≥5% within one or more treatment groups):** Any AE: 58.6% vs 83.9% vs 75.0%; P=0.0006 Nervousness: 17.2% vs 32.3% vs 31.3%; P=0.04 Somnolence: 6.9% vs 41.9% vs 34.4%; P<0.0001 Apathy: 13.8% vs 32.3% vs 18.8% Depression: 17.2% vs 22.6% vs 12.5% Dyspepsia: 24.1% vs 19.4% vs 15.6% Insomnia: 3.4% vs 16.1% vs 12.5% Fatigue: 0.0% vs 22.6% vs 15.6%; P=0.03 Headache: 3.4% vs 16.1% vs 15.6%	Clonidine vs Methylphenidate vs Combination Total withdrawals: 5 (16%) vs 11 (38%) vs 8 (25%); four of the withdrawals in the Methylphenidate group occurred during the first 4 weeks (i.e., before actually receiving methylphenidate -- see intervention column). Due to AE as the primary reason for withdrawal: 1 (3.2%) vs 1 (3.4%) vs 3 (9.4%) Due to AE, not necessarily as the primary reason for withdrawal: 2 (6.9%) vs 1 (3.4%) vs 5 (15.6%)	NINDS grant 5R01 NS039087. Additional NIH support came from K23 MH065375 and K24 AA000301.	Dosing schedule: Clonidine: Initiated with half of a 0.1-mg scored tablet at bedtime, and increased by half of a tablet every 3 days. Dose titration continued until either the optimal dose or the max dose of 0.6 mg/d was reached. Methylphenidate: Started with a 5-mg immediate-release capsule before school. Daily dose allowed to increase by 5 mg every 3 days. Doses were adjusted to optimal effect (max dose 60 mg/d).

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Palumbo 2008/Daviss 2008 US (Fair) (continued)							

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Palumbo 2008/Daviss 2008 US (Fair) (continued)	Treatment Effects on the CGAS: Methylphenidate vs. no methylphenidate: 3.7; 95% CI, -0.2 to 7.5; P=0.06 Clonidine vs. no clonidine: 7.5; 95% CI, 3.6 to 11.4; P=0.0002 Methylphenidate x Clonidine interaction: P=0.02 Methylphenidate vs Clonidine: -3.6; 95% CI, -9.0 to 1.8; P=0.18 Combination vs Methylphenidate: 2.7; 95% CI, -2.6 to 8.1; P=0.32 Combination vs Clonidine: -0.9; 95% CI, -6.2 to 4.4; P=0.73	**Moderate or Severe Adverse Events on Pittsburgh Side Effect Rating Scale** Parent Ratings: Worried/anxious: 3.4% vs 16.1% vs 0.0%; Methylphenidate effect P=0.03 Dull/tired/listless: 6.9% vs 58.1% vs 37.5%; Clonidine effect P<0.0001 Headache: 6.9% vs 19.4% vs 6.3% Stomachache: 10.3% vs 25.8% vs 12.5% Crabby/irritable: 31.0% vs 35.5% vs 31.3% Tearful/sad/depressed: 13.8% vs 19.4% vs 12.5% Socially withdrawn: 6.9% vs 16.1% vs 6.3% Trouble sleeping: 20.7% vs 16.1% vs 12.5% Loss of appetite: 13.8% vs 29.0% vs 9.4% Dizzy/lightheaded: 3.4% vs 6.5% vs 3.1% Dry mouth: 0.0% vs 16.1% vs 6.3%; Clonidine effect P=0.01 Palpitations: 3.4% vs 0.0% vs 0.0% Chest pain: 6.9% vs 0.0% vs 0.0% Sedation/drowsiness: 0.0% vs 54.8% vs 28.1%; Clonidine effect P<0.0001; Methylphenidate effect P=0.08 Teacher Ratings: Worried/anxious: 6.9% vs 12.9% vs 6.3% Dull/tired/listless: 6.9% vs 58.1% vs 31.3%; Clonidine effect P<0.0001 Headache: 6.9% vs 6.5% vs 6.3% Stomachache: 0.0% vs 6.5% vs 3.1% Crabby/irritable: 0.0% vs 12.9% vs 15.6% Tearful/sad/depressed: 6.9% vs 6.5% vs 9.4% Socially withdrawn: 13.8% vs 16.1% vs 15.6% Trouble sleeping: 3.4% vs 9.7% vs 0.0% Loss of appetite: 0.0% vs 3.2% vs 0.0% Dizzy/lightheaded: 0.0% vs 0.0% vs 6.3% Dry mouth: 0.0% vs 0.0% vs 0.0% Palpitations: 0.0% vs 0.0% vs 0.0% Chest pain: 3.4% vs 0.0% vs 0.0% Sedation/drowsiness: 0.0% vs 41.9% vs 21.9%; Clonidine effect P<0.0001			

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Pelham 1987 (Poor)	ADD with or without hyperactivity based on a structured parental interview (not described); teacher ratings on the Swanson, Nolan and Pelham rating scale comprised of DSM-III symptoms; ACTRS and IOWA CTRS scales derived from teacher ratings of the CTRS	Placebo (twice daily) Methylphenidate 20 mg (twice daily) Sustained release methylphenidate 20 mg (once daily) Condition varied daily and 5 to 9 days of data were gathered per medication condition	NR	Mean age=8.8 100% male Race NR	WISC-R IQ=95.3 ACRS Parent/Teacher=17.7/19.0 IOWA CTRS Inattention/Overactivity=11.9 Aggression=8.9 Woodcock-Johnson Achievement Test Reading=91.6 Mathematics=97.0 Language=91.4	13	NR/NR/NR

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pelham 1987 (Poor)	Methylphenidate vs sustained release methylphenidate, t-test, p-value: Daily frequencies Following rules: 3.5 vs 4.3, t=1.8, p=NS Noncompliance: 3.4 vs 4.3, t=-2.5, p<0.05 Positive peer behaviors=100.2 vs 95.8, t=0.8, p=NS Conduct problems: 0.3 vs 0.4, t=-0.4, p=NS Negative verbalizations=3.4 vs 4.8, t=-2.3, p<0.05 N. of time outs/day: 0.5 vs 0.7, t=-1.2, p=NS Classroom % on task=95.2 vs 96.5, t=-0.6, p=NS % on following rules=93.9 vs 92.2, t=0.6, p=NS Timed math No. attempted=21.0 vs 21.7, t=-0.5, p=NS % correct=9.3 4 vs 94.4, t=-0.5, p=NS Timed reading No. attempted=19.8 vs 18.2, t=1.4, p=NS % correct=79.8 vs 77.9, t=0.4, p=NS Seatwork % completion=86.1 vs 89.1, t=-0.9, p=NS % correct=83.7 vs 82.9, t=0.3, p=NS Teacher rating: 1.9 vs 3.4, t=-1.3, p=NS Counselor rating: 106.4 vs 105.9, t=0.1, p=NS Positive daily report card (% of days received): 83.2 vs 81.8, t=0.2, p=NS Observed interactions Positive peer: 97.9 vs 95.2, t=1.6, p=NS Negative peer: 1.4 vs 1.5, t=-0.2, p=NS No interactions: 0.7 vs 3.3, t=-1.8, p=NS	Evidence of anorexia: Standard methylphenidate=4 (30.8%) vs 5 (38.5%); p=NS	NR NR	NR	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Pelham 1990 (Poor)	Diagnosis of ADHD based on structured parental interview and parent and teacher rating scales (not specified)	Methylphenidate IR 20 mg (dosed twice daily) Sustained release methylphenidate 20 mg (dosed once daily) Pemoline 56.25 mg (dosed once daily) Sustained release dextroamphetamine (Dexedrine spansule) 10 mg (dosed once daily) All conditions accompanied by "behavior modification intervention" as the "primary treatment modality" 8 weeks total, data collected for 3 to 6 days for each condition Dosage time NR	NR	Mean age=10.39 100% male Race NR	WISC-R IQ=105.68 ACRS - Parent/Teacher: 15.50/19.32 IOWS CTRS Inattention/Overactivity=9.59 Aggression=5.86 DSM-II-R Structured Interview for Parents Attention deficit disorder items=11.36 Oppositional/defiant disorder items=5.36 Conduct disorder items=1.68 Woodcock-Johnson Achievement Test Reading=96.45 Mathematics=99.82 Language=99.00	22	NR/NR/NR

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pelham 1990 (Poor)	Placebo vs Methylphenidate vs sustained release methylphenidate vs pemoline vs sustained release dextroamphetamine, ALL results significant compared to PLACEBO unless otherwise noted (p=NS): Daily frequency measures: % following activity rules: 75.2 vs 80.9 vs 78.1 vs 79.0 vs 81.0 Noncompliance: 5.5 vs 2.3 vs 2.3 vs 2.0 vs 1.7 Positive peer interactions: 82.8 vs 92.6 (p=NS) vs 104.5 vs 111.1 vs 100.0 Conduct problems: 0.73 vs 0.25 (p=NS) vs 0.18 vs 0.18 vs 0.21 Negative verbalizations: 5.4 vs 1.6 vs 2.0 (p=NS) vs 1.6 vs 1.4 Classroom measures: % following rules: 85 vs 92 (p=NS) vs 94 vs 95 vs 95 Timed reading # attempted: 14.3 vs 18 vs 16.4 vs 15.7 vs 17.5 % correct: 69 vs 73 vs 73 vs 75 vs 74 Seatwork % completed: 70 vs 78 vs 77 vs 79 (p=NS) vs 76 % correct: 84 vs 84 vs 87 (p=NS) vs 87 vs 86 Teacher rating (ACTRS): 3.8 vs 2.3 vs 2.3 vs 1.5 vs 1.7 Counselor rating (ACTRS): 6.3 vs 4.8 vs 5.0 vs 5.1 vs 4.5 Positive daily report (% days rec'd): 51 vs 63 (p=NS) vs 64 vs 71 vs 67	Placebo vs Methylphenidate vs sustained release methylphenidate vs pemoline vs sustained release dextroamphetamine, measures of significance NR: <u>Teacher ratings</u> Withdrawn: 0 vs 10.0 vs 0 vs 0 vs 13.6 Dull, not alert: 4.5 vs 14.3 vs 4.3 vs 0 vs 9.0 Stomachaches, nausea: 13.6 vs 14.3 vs 9.1 vs 10.0 vs 22.7 Headaches: 9.1 vs 0 vs 0 vs 0 vs 22.7 Loss of appetite: 45.0 vs 61.9 vs 76.2 vs 75 vs 77.3 Eye/Muscle twitches: 4.5 vs 4.8 vs 9.1 vs 4.89 vs 4.5 Repetitive tongue movements: 9.1 vs 4.8 vs 0 vs 5.0 vs 4.5 Picking: 0 vs 0 vs 0 vs 0 vs 4.5 <u>Parent ratings</u> Difficulty falling asleep: 5.3 vs 5.9 vs 18.8 vs 42.1 vs 20.0 Awake during the night: 5.3 vs 12.5 vs 13.3 vs 11.1 vs 14.3	NR NR	NR	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Pelham 1999a (Fair)	DSM-IV diagnosis of ADHD	MPH=methylphenidate 1) placebo at 7:30 am, 11:30 am, and 3:30 pm 2) 0.3 mg/kg of MPH at 7:30 am, 11:30 am, and 3:30 pm 3) 0.3 mg/kg of MPH at 7:30 am and 11:30 am with 0.15 mg/kg at 3:30 pm 4) 0.3 mg/kg of MPH at 7:30 am only 5) 0.3 mg/kg of Adderall at 7:30 am and at 3:30 pm 6) 0.3 mg/kg of Adderall at 7:30 am with 0.15 mg/kg received at 3:30 pm 7) 0.3 mg/kg of Adderall at 7:30 am only Medication received Monday through Thursday throughout a period of 6 weeks for a 24-day clinical medication assessment; resulting in ~3 days of data in each of the active drug conditions and 6 days in the placebo condition	Concurrent behavioral point system	Mean age=10.3 90.5% male Race NR	87% with previous use of stimulant medication 9 (43.8%) with learning problems 14 (66.7%) with comorbid ODD 5 (23.8%) with comorbid conduct disorder Mean IQ=109.9 Reading achievement standard score=99.1 Math achievement standard score=105.7 ADHD items endorsed in parent structured interview: Inattention (out of 9 items)=6.1, Hyperactivity/impulsivity (out of 9 items)=5.5 oppositional/defiant items endorsed in parent structured interview=4.3 Conduct disorder items endorsed in parent structured interview=2.8 Abbreviated Conners rating scale parent=20.5 Abbreviated Conners rating scale teacher=18.2 IOWA Conners teacher rating scale inattention-overactivity/oppositional-defiant: 9.6/7.5 Disruptive behavior disorders parent rating scale: Inattention=2.2, Hyperactivity/impulsivity=2.0, Oppositional/defiant=1.8, Conduct disorder=0.4 Disruptive behavior disorders teacher rating scale: Inattention=1.7, Hyperactivity/impulsivity=1.7, Oppositional/defiant=1.6	21	NR/NR/NR

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pelham 1999a (Fair)	Adderall q AM vs MPH bid vs MPH q AM b = p<0.05 vs MPH bid; c = p<0.05 vs MPH q AM Counselor measures Following activity/rules: 73.1c vs 70.6 vs 65.7b Noncompliance: 1.2 vs 0.8 vs 1.2 Interruption: 4.0 vs 5.3 vs 6.9 Complaining: 3.0 vs 3.0 vs 5.8b Positive peer behaviors: 5.5 vs 5.2 vs 6.4 Conduct problems: 1.7 vs 0.9 vs 0.6 Negative verbalizations: 3.6 vs 3.9 vs 6.6 IOWA Conners IQ: 3.0c vs 3.3c vs 4.3 IOWA Conners OD: 1.9c vs 2.2c vs 3.1 Classroom measures: Seatwork rules: 92.7 vs 91.9 vs 84.6 Peer tutoring rules: 93.9 vs 93.6 vs 90.1 Computer rules: 92.3 vs 93.4 vs 89.3 Seatwork complete: 90.2 vs 86.1 vs 86.9 Seatwork correct: 90.9 vs 89.8 vs 87.5 On-task behavior: 97.1 vs 96.1 vs 94.9 Disruptive behavior: 1.9 vs 2.5 vs 3.5 Teacher IOWA Conners IO: 0.8c vs 0.9 vs 2.0b Teacher IOWA Conners OD: 0.7 vs 0.4 vs 1.4b Daily Report Card: 82.8c vs 80.5 vs 69.0	% children rated by Counselor/Parent/Teacher as displaying side effects at a moderate-severe leve on at least one day: MPH q AM vs MPH 0.3/0.3/0.15 vs MPH 0.3/0.3/0.3 vs Adderall q AM vs Adderall 0.3/-/0.15 vs Adderall 0.3/-/0.3 Tics: 5/10/5 vs 5/10/0 vs 5/10/5 vs 5/5/0 vs 5/0/5 vs 5/0/5 vs 0/5/0 Appetite loss: 5/25/- vs 57/20/0 vs 33/33/- vs 29/33/- vs 71/15/- vs 62/29/- vs 52/29/- Sleep trouble (only parent ratings): 25 vs 15 vs 20 vs 20 vs 24 vs 38 vs 33	NR NR	Shire	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Pelham 1999b (Fair)	DSM-IV diagnosis of ADHD	Adderall 7.5 mg at 7:45 am and 12.5 mg at 12:15 pm Methylphenidate 10 mg at 7:45 am and 17.5 mg at 12:15 pm Medication received Monday through Thursday throughout a period of 6 weeks for a 24-day clinical medication assessment; resulting in ~5 days of data in each of the active drug conditions and 6 days in the placebo condition	NR	Mean age=9.6 84% male 88% white	13 (52%) with comorbid oppositional defiant disorder 8 (32%) with comorbid conduct disorder WISC vocabulary scaled score=12.3 WISC block design scaled score=11.2 WIAT spelling scaled score=95.7 WIAT math scaled score=105.7 DSM ADHD items-parent=10.8 DSM ODD items-parent=5.3 DSM CD-parent=1.8 Abbreviated Conners-parent=22.6 Abbreviated Conners-teacher=19.6 Iowa Conners I/O-teacher=11.8 Iowa Conners O/D-teacher=9.6 Disruptive behavior disorders parent/teacher rating scale: ADHD=1.5/2.4 Oppositional/defiant=1.7/2.5 Conduct disorder=1.8/nr	25	NR/NR/NR

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pelham 1999b (Fair)	Adderall 7.5/12.5 vs Methylphenidate 10 mg/17.5 mg; results of ANOVA of methylphenidate vs Adderall; p-value: Classroom variables Rule-following Seatwork: 89.7/90.7 vs 84.3/87.8, 4.06, p=NS Peer tutoring: 95.1/95.0 vs 91.4/94.8, 3.71, p=NS Computer: 91.1/94.4 vs 87.3/92.6, 2.80, p=NS Seatwork completion: 71.6/67.1 vs 69.5/69.2, 0.00, p=NS Seatwork accuracy: 87.6/87.3 vs 87.9/87.1, 0.00, p=NS Observational measures On-task behavior: 89.0/89.9 vs 89.2/89.6, 0.00, p=NS Disruptive behavior: 6.4/6.4 vs 6.9/6.2, 0.15; p=NS Daily report card: 83.8/82.8 vs 76.4/81.7, 6.63, p<0.05 Recess rule violations: 1.0/0.4 vs 1.3/0.7, 3.21, p=NS Counselor ratings I/O: 2.4/2.2 vs 3.4/2.6, 1.4, p<0.001; O/D: 1.0/0.8 vs 2.3/1.1, 13.85, p<0.01 Teacher ratings I/O: 1.2/1.2 vs 1.8/1.1, 0.72, p=NS; O/D: 0.7/0.4 vs 1.3/0.6, 3.22, p=NS 5:00-6:00 parent ratings I/O: 0.9/0.5 vs 1.5/1.0, 5.25, p<0.05; O/D: 0.8/0.6 vs 1.2/1.1, 4.09, p=NS All evening parent ratings I/O: 1.5/1.4 vs 2.6/1.7, 3.33, p=NS; O/D: 1.9/1.2 vs 2.4/1.2, 12.17, p<0.01 Point system measures Following rules: 75.4/79.9 vs 71.4/74.5, 10.38, p=NS Attention: 68.2/68.2 vs 64.0/64.3, 5.47, p=NS Noncompliance: 0.9/1.2 vs 2.2/0.8, 5.65; p=NS Interruption: 6.2/6.8 vs 10.6/6.7, 7.48, p=0.025 Complaining/whining: 2.9/2.0 vs 4.1/2.6, 4.12, p=NS Positive peer behaviors: 8.1/7.8 vs 8.8/8.8, 1.82, p=NS Conduct problems: 0.4/0.2 vs 1.4/0.1, 5.17, p=NS Negative verbalizations: 2.0/2.2 vs 6.1/2.2, 7.89, p=0.01	% children rated by Counselor/Parent as displaying side effects at a moderate-severe leve on at least one day: Adderall 7.5 mg vs Adderall 12.5 mg vs methylphenidate 10 mg vs methylphenidate 17.5 mg Motor Tics Counselors: 8 vs 8 vs 8 vs 4 Parents: 4 vs 8 vs 4 vs 0 Trouble sleeping Counselors: n/a Parents: 48 vs 64 vs 32 vs 24 Loss of appetite Counselors: 76 vs 80 vs 60 vs 68 Parents: 40 vs 72 vs 8 vs 20	1 (4%) withdrawal due to exacerbation of pre-existing motor tics	Shire	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Pelham 2001 (Fair)	Children between the ages of 6 and 12 with a DSM-IV diagnosis of ADHD (any subtype). Children met DSM diagnostic criteria using a rule in which a symptom was defined as present if either parents or teachers endorsed it, with overlap between raters on at least 1 symptom. Medicated with a stable dose of methylphenidate for at least 4 weeks before the beginning of the study	Placebo Methylphenidate immediate release, three times daily (7:30 AM, 11:30 AM, 3:30 PM), average dose=29 mg (0.88 mg/kg) Methylphenidate extended release (Concerta), once daily in the morning (7:30 AM), average dose=35 mg (1.05 mg/kg) Flexible dosing determined based on that child's MPH dosing before the study Double-dummy placebo design 7 days, then crossover	4-6 sessions of behavioral parent training was provided (how to use behavioral techniques in the home setting); teacher received 1-4 clinical contacts during which a consulting teacher worked with each child's teacher to establish a daily report card (DRC) and to consult on other classroom management strategies	Mean age 9.1 89% male 94% white	Pre-study MPH use: BID dosing=57%; TID dosing=43% Full-scale IQ (WISC-III)=104.8 Reading achievement (WIAT)=104.1 Math achievement (WAIT)=98.8 Spelling achievement (WIAT)=96.3 DISC hyperactive/impulsive symptoms=8.3 DISC inattention symptoms endorsed=7.1 Parent SNAP ratings Inattention=2.26 Hyperactivity/impulsivity=1.96 Oppositional/defiant=1.56 Parent/DBD Ratings Inattention=2.15 Hyperactivity/impulsivity=1.83 Oppositional/defiant=1.28 Conduct disorder=0.26 Parent IOWA Conners ratings Inattention/overactivity=10.42 Oppositional/defiant=7.28 Parent abbreviated Conners rating=18.06 Teacher SNAP ratings Inattention=2.04 Hyperactivity/impulsivity=1.62 Oppositional/defiant=1.56 Teacher DBD ratings Inattention=1.82 Hyperactivity/impulsivity=1.47 Oppositional/defiant=0.75	70	2 (2.8%) withdrawn/lost to fu NR/analyzed 68 5 children missed one of 3 testing sessions

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pelham 2001 (Fair)	Placebo / tid IR MPH / Concerta, p-value = MPH IR vs Concerta Natural setting Teacher ratings Inattention/overactivity: 10.34 vs 5 vs 4.69, p=NS; Oppositional/defiant: 5.09 vs 1.99 vs 1.81, p=NS Abbreviated Conners; 16.40 vs 7.4 vs 7.82, p=NS; Peer interactions: 4.29 vs 4.03 vs 3.41; p=NS Global effectiveness: NS on any classification Daily report card (% positive): 61.17 vs 84.36 vs 86.06 Parent ratings Inattention/overactivity: 10.59 vs 5.93 vs 4.78; p=0.05; Oppositional/defiant: 8.85 vs 5.26 vs 4.82; p=NS Abbreviated Conners: 19.91 vs 11.41 vs 9.49; p=0.05 Global effectiveness: Poor: 73.5% vs 8.8% vs 5.9%; p=NS; Fair: 22.1% vs 26.5% vs 27.9%, p=NS Good: 2.9% vs 50.0% vs 39.7%, p=NS; Excellent: 1.5% vs 14.5% vs 26.5%, p=NS (p=NS for all remaining comparisons of tid IR MPH vs Concerta) Recreational Activities -- Counselor measures Rule violations (mean #)-- 7:45-8:10: 2.52 vs 2.83 vs 2.21; 9:55-10:25: 4 vs 2.58 vs 2.70 1:25-1:55: 5.87 vs 2.17 vs 2.39; 4:35-5:00: 5.21 vs 2.84 vs 2.53 Negative behavior (mean #)-- 7:45-8:10: 1.53 vs 4.86 vs 1.73; 9:55-10:25: 3.62 vs 1.14 vs 1.14 1:25-1:55: 6.25 vs 0.98 vs 2.45; 4:35-5:00: 4.76 vs 2.83 vs 1.58 Individual target goals-- 7:45-8:10: 79.05 vs 69.01 vs 75.13; 9:55-10:25: 65.44 vs 82.30 vs 78.91 1:25-1:55: 56.13 vs 81.25 vs 74.22; 4:35-5:00: 58.82 vs 76.43 vs 80.73 Observer measure negative behavior-- 7:45-8:10: 3.24 vs 4.00 vs 4.21; 9:55-10:25: 6.99 vs 2.13 vs 2.97 1:25-1:55: 8.96 vs 2.17 vs 3.47; 4:35-5:00: 8.91 vs 4.61 vs 2.86	Placebo vs QD Concerta vs tid IR MPH Serious adverse events: 0 vs 0 vs 0 Motor tics: 0 vs 4/70 (5.7%) vs 0 Sleep(% patients) Excellent: 12% vs 13% vs 7% Good: 57% vs 47% vs 65% Fair: 21% vs 24% vs 21% Poor: 10% vs 16% vs 7% Usual appetite: 59% vs 77% vs 66% Appetite loss: 4: vs 18% vs 24% Headache: 16 (23.2%) vs 8 (11.8%) vs 11 (15.9%) Abdominal pain: 8 (11.6%) 9 (13.2%) vs 12 (17.4%) Upper respiratory tract infection: 3 (4.3%) vs 2 (2.9%) vs 3 (4.3%) Accidental injury: 2 (2.9%) vs 1 (1.5%) vs 3 (4.3%) Vomiting: 2 (2.9%) vs 2 (2.9%) vs 2 (2.9%) Twitching: 0 vs 0 vs 4 (5.8%) Diarrhea: 1 (1.4%) vs 0 (0.0%) vs 2 (2.9%) Pharyngitis: 0 (0.0%) vs 1 (1.5%) vs 2 (2.9%) Rhinitis: 0 (0.0%) vs 1 (1.5%) vs 2 (2.9%) Dizziness: 0 (0.0%) vs 2 (2.9%) vs 1 (1.4%) Urinary incontinence: 2 (2.9%) vs 0 (0.0%) vs 1 (1.4%)	2 (2.8%) withdrawals overall (group assignment unclear) Withdrawals due to adverse events: none reported	Alza	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Pelham 2001 (Fair) Continued.					Teacher IOWA Conners ratings Inattention/overactivity=9.65 Oppositional/defiant=4.07 Teacher abbreviated Conners rating=14.96 Teacher peer relations rating=5.33		
Pelham 2011 US (Fair)	Boys (girls were eligible but none enrolled) ages of 7-9 years with ADHD, an estimated full-scale IQ of at least 80, and who were receiving a stable dose of IR MPH before enrollment.	A: MTS 20 cm2 worn for 24 hours B: IR MPH 10 mg tid C: Placebo for 3 weeks (within-subject, random crossover design)	NR	Age: 8.6 years (SD 1.1) Male: 100% White: 50% Black: 20% Native American: 10% Other: 20%	IQ score: 95.3 (SD 9.9) Combined subtype of ADHD: 80% Inattentive subtype of ADHD: 20% Patients also meeting criteria for ODD or CD: 80%	10	1/0/9

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pelham 2001 (Fair) Continued.	Recess measures (means) Rule violations-- 11:05: 0.81 vs 0.44 vs 0.36; 2:50: 1.10 vs 0.66 vs 0.52; 7:45: 2.07 vs 1.42 vs 1.53; Negative behavior-- 11:05: 10.37 vs 7.48 vs 8.56; 2:50: 14.03 vs 10.13 vs 7.65; 7:45: 13.76 vs 8.88 vs 7.73 Laboratory sessions (means) (overall daily measures) Behavior frequencies Following rules: 47.5% vs 60.2% vs 61.3%; Noncompliance: 5.76 vs 2.73 vs 2.14 Interruption: 21.6 vs 10.5 vs 10.58; Complaining/whining: 15.45 vs 6.95 vs 6.67 Positive peer behaviors: 10.52 vs 9.86 vs 9.20; conduct problems: 3.81 vs 1.53 vs 0.60 Negative verbalizations: 18.27 vs 9.29 vs 7.14 Teacher rating-- Inattention/overactivity: 5.01 vs 2.75 vs 2.59; Oppositional/defiant: 2.18 vs 1.19 vs 1.30 Abbreviated Conners: 7.03 vs 4.03 vs 3.75; Peer interactions: 0.24 vs 0.15 vs 0.15 Counselor rating-- Inattention/overactivity: 7.95 vs 6.31 vs 6.10; Oppositional/defiant: 3.63 vs 2.58 vs 2.36 Abbreviated Conners: 12.70 vs 9.91 vs 9.26; Peer interactions: 0.77 vs 0.56 vs 0.49				
Pelham 2011 US (Fair)	Placebo vs MTS vs MPH tid Rule violations, mean (SD): 81.3 (62.1) vs 40.4 (52.4; MTS vs placebo F(1,8)=9.96, P=0.01) vs 45.3 (41.3; MPH tid vs placebo F(1,8)=15.59, P<0.01); MTS vs MPH tid F(1,8)=0.35, P=NS Math correct, mean (SD): 21.6 (25.0) vs 29.6 (22.7; MTS vs placebo F(1,8)=5.14; P=0.05) vs 34.3 (29.7; MPH tid vs placebo F(1,8)=30.86, P<0.001); MTS vs MPH tid F(1,8)=1.12, P=NS Inattention/overactivity teacher rating: 9.7 (5.1) vs 5.8 (4.9; MTS vs placebo F(1,8)=8.83, P=0.02) vs 6.0 (4.3; MPH tid vs placebo F(1,8)=8.50, P=0.0195); MTS vs MPH tid F(1,8)=0.02, P=NS Oppositional–defiant teacher rating: 9.0 (5.0) vs 4.8 (5.3; MTS vs placebo F(1,8)=9.18, P=0.02) vs 4.7 (4.3; MPH tid vs placebo F(1,8)=12.24, P<0.01); MTS vs MPH tid F(1,8)=0.00, P=NS	NR by treatment group Parent-reported appetite reduction: 33% on IR MPH or MTS vs 22% on placebo There was only one case of emotional lability reported which occurred during MTS usage. Five events were recorded as moderate in severity, one for IR MPH (malaise), none for MTS, and four in the placebo condition (vomiting, stomach ache, faintness, and flu-like symptoms).	Placebo vs MTS vs MPH tid Total withdrawals: 1 (10%) vs 0 vs 0 Due to AE: 0 vs 0 vs 0	Noven Pharmaceuticals	The doses of IR MPH and MTS were deemed to be equivalent based on data from the development of the MTS (33 mg/24 hr for MTS vs. 30 mg/24 hr for IR MPH).

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Pliszka 2000/Faraone 2001 (Fair)	DISC criteria for ADHD; ≥ 1.5 SD above the mean for his/her age and sex on the IOWA CTRS Inattention/Overactivity (I/O) factor; parent Conners Global Index score similarly elevated	Adderall < 60 kg = 5-15 mg > 60 kg = 10-30 mg Week1: single am dose Week2: morning dose doubled if no improvement on morning+afternoon or just afternoon teacher ratings; after school dose added if morning+afternoon teacher ratings improved, but parent rating remained impaired Week3: noon dose added if afternoon behavior remained impaired; after school dose added if evening behavior had not been impaired in week 1 but now was Methylphenidate < 60 kg = 5-25 mg > 60 kg = 10-50 mg Week1: single am dose Week2: morning dose doubled if no improvement on morning+afternoon (teacher); noon dose added if no afternoon improvement (teacher); after school dose added if evening rating (parent) remained impaired; morning dose doubled and a noon dose added if morning+afternoon teacher ratings Week3: noon dose doubled if the afternoon ratings (teacher) remained impaired 3 weeks; Flexible dosing and timing	NR	Mean age=8.2 Gender NR Race NR	IOWA CTRS I/O: 2.2 IOWA CTRS A/D: 1.4 Conners Global: 2.1 ODD=62% CD=10.3% Anxiety disorder=12.1% RCMAS: 15.8% CDI: 12.2% Weight (kg): 33.3	58	5 (8.6%) withdrawn/0 lost to fu/58 analyzed Adderall n=20 Methylphenidate n=20 Placebo n=18

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pliszka 2000/Faraone 2001 (Fair)	Adderall vs methylphenidate IOWA CTRS I/O: AM: 0.44 vs 0.78; p=NS PM: 0.54 vs 0.85, p=NS Average: 0.49 vs 0.81, p<0.05 IOWA CTRS A/D AM: 0.25 vs 0.47, p=NS PM: 0.33 vs 0.51, p=NS Average: 0.29 vs 0.49, p<0.05 Conners Global Index: 1.04 vs 1.28, p=NS CGI Improvement: 1.6 vs 2.35, p<0.05 Responders %: 90 vs 65 Final weight (kg): 37 vs 33.2, p=NS Dosing regimen: 70% of Adderall subjects required only an AM dose vs 85% in the methylphenidate group received 2 or more doses per day; p=0.003	All p=NS Facial tics: 1 (5%) vs 0 Tongue movements: 1 (5%) vs 0 Picking at skin: 1 (5%) vs 0 Anxious: 1 (5%) vs 2 (10%) Tired: 2 (10%) vs 4 (20%) Headache: 2 (10%) vs 0 Stomach ache: 5 (25%) vs 1 (5%) Irritable: 5 (25%) 3 (15%) Sad, tearful: 5 (25%) vs 3 (15%) Appetite loss: 3 (15%) vs 3 (15%) Gets wild when medication wears off: 7 (35%) vs 8 (40%)	Total withdrawals=5 (8.6%) Withdrawals due to adverse events: 2 (10%) vs 1 (5%), p=NS	Shire	

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Prasad 2007 (Poor)	Patients were children and adolescents who met DSM-IV criteria for ADHD by clinical investigator assessment and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Versions (K-SADS-PL). Children were 7–15 years of age, and were not intellectually impaired in the viewpoints of the investigators. They were required to have a symptom severity score ≥ 1.5 standard deviations above the investigator-rated ADHD-Rating Scale-IV (ADHD-RS) age norm for their ADHD subtype to be eligible for enrolment. Patients were assessed for other psychiatric disorders by clinical assessment and by the K-SADS-PL (disruptive behaviors, anxiety, and affective disorders modules).	Atomoxetine: Mean Dose: 1.5 mg/kg/day. commenced on 0.5 mg/kg/day. After a minimum of 7 days, patients who, in the judgment of the investigator, had clinically significant residual symptoms and who were tolerating atomoxetine, could have a dose increase to approximately 1.2 mg/kg/day. After a minimum of two further weeks, a dose increase to a maximum of 1.8 mg/kg/day was permitted, if required, based on the investigator's assessment of clinical response (efficacy and tolerability) SCT: Mean daily dose of single therapy short acting MPH was 0.80 mg/kg/day, and for long-acting OROS MPH was 1.03 mg/kg/day. SCT was defined as any intervention regarded by the investigator/treating physician that would benefit the patient, and that they would use as appropriate in their standard clinical practice, including the option of no therapy. SCT could include any combination of medicines (apart from atomoxetine) and/or simple behavioral counseling approaches	NR	Mean age: 10.9 yrs (SD 2.2) (Range: 6.9-15.9 yrs) 88.6% male 99% Caucasian	Atomoxetine vs SCT Previously treated with stimulants: 59.6% vs 70.1%, p=0.140 patients that have not previously taken any medication: 27.96% vs 19.6%, p=0.187 Pts that have taken medications other than stimulants: 13 pts vs 10 pts, p=0.663 <u>ADHD subtype:</u> Combined: 181(90.5%), p=0.055 Hyperactive: 4(2%), p= >0.999 Inattentive: 15(7.5%), p=0.030 <u>Other disorders in >5% patients:</u> Oppositional defiant disorder: 124(61.7%), p=0.563 Conduct disorder: 14(7%), p= >0.999	201	7 withdrew in study period I, 26 in atomoxetine group withdrew in study period II, 6 SCT pts withdrew in study period II,

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Prasad 2007 (Poor)	No differential treatment effect between SCT and atomoxetine. LS mean ± SE of the total score of the CHIP-CE increased to 38.4± 1.3 for atomoxetine and to 30.8±1.3 for the SCT group patients treated with atomoxetine was superior in health compared with SCT patients. Atomoxetine patients was just greater than one SD below the US norm of 50. Overall treatment effect for atomoxetine was significant (p<0.001) No significant difference in reduction of FBIM total score between atomoxetine vs SCT Improved investigator-rated ADHD-RS score was higher for atomoxetine pts at wk 10 (p<0.001)	Atomoxetine vs SCT headache: 22(21.2%) vs 8(8.2%), p=0.016 Nausea: 18 (17.3%) vs 3(3.1%), p= <0.001 Weight decreased: 8 (7.7%) vs 8(8,2%), p= >0.999 Decreased appetite: 8(7.7%) vs 6(6.2%), p=0.784 Vomiting: 9(8.7%) vs 2(2.1%), p=0.059 Abdominal pain upper: 7(6.7%) vs 3(3.1%), p=0.334 Cough: 6(5.8%) vs 4(4.1%), p=0.749	Total withdrawals depends on the phase of the study; 6 withdrawals due to adverse events	Eli Lilly	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Sangal 2006 US (Poor)	Patients were 6 to 14 years old at study entry. They were diagnosed with ADHD using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria as well as severity criteria. Diagnosis was assessed by the investigator's clinical evaluation and by the administration of several modules of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version structured interview. In addition, patients had an ADHD Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS) score at least 1.0 standard deviation above normative values for age and sex for either the inattentive or hyperactive/impulsive subscore, or for the combined score. All patients scored at least 80 on the Wechsler Intelligence Scale for Children -3rd edition.	Atomoxetine Mean final dose: 58.27 mg/day (range = 15-100), or 1.56mglkg per day Methylphenidate: Mean final dose was 42.29 mg/day (range = 15-60), or 1.12 mg/kg per day	NR	Mean age: 10.1 yrs (SD 2.0) 75.3% male 72.9% Caucasian	ADHD Subtype: Hyperactive/Impulsive: 2.4% Inattentive: 29.8% Combined: 67.9% Present Comorbid Conditions: ODD: 48.2% Conduct Disorder: 3.5% Anxiety Agoraphobia: 1.2% Prior stimulant exposure: 56.5%	85	6 withdrew after 1st acute treatment phase; 4 withdrew after 2nd acute treatment phase 50 analyzed (25 excluded from analysis) n=79 for safety

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Sangal 2006 US (Poor)	Actigraphic Sleep Measures Change from Baseline (SD) Atomoxetine vs. Methylphenidate; [95% CI] Sleep-onset latency, min: 12.06 (27.07) vs. 39.24 (40.77); p<0.001 [-12.82, -6.49] Total nap time, min: 4.49 (10.41) vs. 3.04 (7.92); p=0.475 [-1.68, 3.55] Total sleep interval, min: -15.00 (45.10) vs. -35.89 (56.10); p=0.004 [6.81, 34.15] Assumed sleep time, min: -15.26 (44.25) vs. 29.61 (53.00); p=0.016 [2.73, 25.73] Interrupted sleep time, min: 0.26 (15.04) vs. -6.28 (17.48); p=0.025 [0.80, 11.69] Sleep interruptions, no.: -1.31 (6.83) vs. -4.36 (6.33); p=0.011 [0.70, 5.19]	TEAs occurring in at least 10% of the 79 patients in either treatment group (Atomoxetine vs. Methylphenidate) Decreased appetite: 11.4% vs. 24.1% (p=0.30) Headache: 19.0% vs. 15.2% (p=0.698) Insomnia: 6.3% vs. 26.6% (p<0.001) Appetite decreased: 11.4% vs. 15.2% (p=0.357) Irritability: 11.4% vs. 15.2% (p=0.263) Pharyngitis: 15.2% vs. 8.9% (p=0.173) Cough: 12.7% vs. 8.9% (p=0.625) Somnolence: 15.2% vs. 3.8% (p=0.057) Abdominal pain, upper: 11.4% vs. 5.1% (p=0.248) Fatigue: 11.4% vs. 3.8% (p=0.121)	No withdrawals due to adverse events; total withdrawals depends on which phase of the study	Sponsored by Eli Lilly; data were analyzed by statisticians at Eli Lilly.	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Schachar 2008 Canada (Fair)	Patients were aged 6-15 years with a diagnosis of ADHD according to the DSM-IV, with an IQ of ≥85 on the Wechsler Intelligence Scales for Children within the previous 12 months, must be mentally and physically competent to give consent. Patients were excluded if they were allergic to MPH or amphetamines or had a history of serious adverse reactions to MPH or had a lack of response to MPH; if they had serious or unstable medical illness, co-morbid psychiatric illness of sufficient severity to require treatment, or currently receiving psychotropic medications or herbal treatments; and if they had disorders of the sensory organs, autism, psychosis, or any unstable psychiatric conditions.	MPH 1.2mg/kg per day (average daily dose=31.2mg/day; range: 20-60mg/day) Multi-layer release was given as a single morning dose, with placebo at lunch-time (MLR MPH) Immediate release was given as two equal doses at morning and lunch-time (IR MPH) Placebo was given at both morning and lunch-time (Placebo)	NR	Mean age: 11.3 years 88% male Ethnicity: NR	NR	18	1 withdrew, none were lost to follow-up 17 analyzed

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Schachar 2008 Canada (Fair)	Placebo vs IR MPH vs MLR MPH (mean) Stop task - go task (msec): 721.8 vs 670.9 vs 673.1 Stop task - mean delay (msec): 349.6 vs 409.3 vs 426.1 Stop task - stop signal reaction time (msec): 372.2 vs 261.6 vs 247.1 Continuous performance test - errors of omission (n): 60 vs 31 vs 47.7 Continuous performance test - errors of commission (n): 24.1 vs 25.6 vs 24.5 Arithmetic test - number completed: 22.9 vs 26 vs 20.5 Arithmetic test - number correct: 17.6 vs 20.7 vs 20.5 Arithmetic test - percent correct: 75.8% vs 77.5% vs 81.2% IOWA-C - overall change from baseline: 2.03 vs -0.66 vs -1.38 IOWA-C - Inattention/overactivity subscale change from baseline: 3.20 vs -0.98 vs -1.26 IOWA-C - Aggression/defiance subscale change from baseline: 0.86 vs -0.33 vs -1.5 Problem situations change from baseline: 1.49 vs -0.35 vs -0.47 Communicative pragmatics change from baseline: 2.91 vs -0.27 vs -0.89 CGI of "much improved" or "very much improved": 17.6% vs 58.8% vs 76.5%	MLR MPH vs IR MPH vs Placebo Headache: 1 vs 1 vs 1 Tremor: 0 vs 1 vs 1 Somnolence: 1 vs 1 vs 0 Asthenia: 1 vs 0 vs 0 Psychosis: 0 vs 0 vs 1 Anorexia: 0 vs 1 vs 0 Rhinitis: 0 vs 1 vs 0 Infection: 0 vs 0 vs 1 Pruritus: 0 vs 1 vs 0	1 withdrew, none due to AEs	Some authors are employed by or receive money from Purdue Pharma, but study was not sponsored by Purdue Pharma	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Sharp 1999 (Fair)	Girls with ADHD symptoms present in at least 2 settings; Conners Hyperactivity factor scores from their home teacher were at least 2 SD greater than age and sex norms	Mean doses for weeks 1, 2, and 3: Dextroamphetamine 0.23, 0.43, and 0.64 mg/kg Methylphenidate 0.45, 0.85 and 1.28 mg/kg Twice daily: breakfast and lunch 3 weeks, then crossover	All subjects attended accredited NIMH school 5 days a week for 3 months (academic instruction in the morning and recreation therapy activities in the afternoon)	n=42 (includes 10 girls from another, unpublished pilot trial of sustained release dextroamphetamine vs Adderall) Mean age=8.9 100% female 67% white, 19% black, 14% Latina	n=42 (includes 10 girls from another, unpublished pilot trial of sustained release dextroamphetamine vs Adderall) SES: 48 WISC-R Full Scale IQ=105.2 WISC-R Verbal IQ=105.6 WISC-R Performance IQ=104.0 WJ Reading/Math standard scores: 95.6/96.6 C-GAS=44.6 CGI-SI=5 Teacher/Parent Conners: Hyperactivity=2.0/2.5; Conduct=0.9/1.4 CBCL: Attention problems=76.0, Externalizing behaviors=70.7, Internalizing behaviors=63.6, Total behaviors=71.0 TRF: Attention problems=70.3, Externalizing behaviors=69.7, Internalizing behaviors=61.0, Total behavior problems=69.3	32	1 (3.1%) withdrawn/lost to fu NR/analyzed=32

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Sharp 1999 (Fair)	% patients with CGI--GI ratings of "very much improved" or "much improved": 85% vs 83%; p=NS	Mean change in body weight (kg) Dextroamphetamine: -1.1; p=0.01 from baseline Methylphenidate: -0.4; p=NS from baseline	1 (3.1%) total withdrawals Withdrawals due to adverse events NR	NR	Meta-analysis of this 100% female trial

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Silva 2005 US (Fair)	Eligible participants were children 6–12 years of age who met DSM-IV (C-DISC-4 1997) criteria for a primary diagnosis of ADHD and whose parents provided written consent for their participation in the study. Assent to participate was also obtained from all children. Inclusion criteria required that children were treated and stabilized on a total daily dose of 20–40 mg MPH for at least 2 weeks prior to enrollment. Female participants were required to be premenarchal, sexually abstinent, or using an approved method of contraception; those of childbearing potential were required to have a negative urine pregnancy test prior to enrollment.	single doses of extended-release MPH (ER-MPH) 20 and 40 mg, modified-release MPH (OROS-MPH) 18 and 36 mg, and placebo Mean Dose: NR	NR	Mean age: 9.4 yrs (SD 1.9) 63% male 63% Caucasian 14.8% African American 0% Asian 22.2% other	ADHD subtype Inattentive: 27.8% Hyperactive/impulsive: 1.9% Combined inattentive/hyperactive: 70.4%	54	1 withdrew

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Silva 2005 US (Fair)	Mean (SD) Postdose Scores (ER-MPH 20mg/ER-MPH 40mg/OROS-MPH 18mg/OROS-MPH 36mg/placebo) SKAMP-Attention (hours postdose) 0.5-hr: 1.70 (0.73)/1.78 (0.94)/1.97 (0.97)/1.79 (0.93)/1.86 (1.03) 1.0-hr: 1.37 (1.04)/1.37 (1.03)/1.70 (1.07)/1.76 (1.13)/2.26 (1.17) 2.0-hr: 1.08 (0.78)/0.89 (0.81)/1.31 (0.97)/1.63 (1.10)/1.79 (1.17) 3.0-hr: 1.30 (0.85)/1.01 (0.80)/1.50 (1.01)/1.65 (1.16)/2.08 (1.03) 4.0-hr: 1.31 (0.81)/1.28 (0.88)/1.57 (1.02)/1.49 (0.86)/1.95 (1.00) 6.0-hr: 1.47 (0.85)/1.21 (0.98)/1.55 (0.94)/1.60 (0.99)/2.09 (0.93) 8.0-hr: 1.75 (0.84)/1.41 (1.01)/1.64 (1.04)/1.62 (0.97)/2.18 (1.07) 10.0-hr: 1.84 (0.93)/1.74 (1.04)/1.56 (0.91)/1.81 (1.14)/2.20 (1.10) 12.0-hr: 2.13 (0.98)/1.89 (0.83)/1/73 (1.09)/1.53 (1.06)/2.22 (0.98) SKAMP-Deportment (hours postdose) 0.5-hr: 1.37 (1.29)/1.19 (1.16)/1.48 (1.21)/1.46 (1.38)/1.74 (1.49) 1.0-hr: 1.12 (1.17)/0.79 (1.08)/1.39 (1.31)/1.33 (1.42)/2.10 (1.52) 2.0-hr: 0.91 (0.95)/0.48 (0.65)/1.07 (1.12)/1.19 (1.30)/2.06 (1.46) 3.0-hr: 0.96 (0.93)/0.58 (0.74)/1.27 (1.15)/1.09 (1.10)/2.15 (1.52) 4.0-hr: 1.12 (1.05)/0.63 (0.77)/1.36 (1.24)/1.12 (1.13)/2.19 (1.41) 6.0-hr: 1.20 (1.02)/0.70 (0.83)/1.37 (1.13)/1.16 (1.25)/2.14 (1.24) 8.0-hr: 1.36 (1.29)/0.92 (1.04)/1.35 (1.09)/1.39 (1.33)/2.00 (1.30) 10.0-hr: 1.65 (1.23)/1.25 (1.18)/1.40 (1.28)/1.27 (1.24)/2.06 (0.98) 12.0-hr: 1.94 (1.21)/1.54 (1.19)/1.54 (1.25)/1.33 (1.17)/2.14 (1.29) SKAMP-Combined (hours postdose) 0.5-hr: 1.52 (0.89)/1.46 (0.94)/1.70 (0.95)/1.61 (1.03)/1.79 (1.17) 1.0-hr: 1.24 (0.96)/1.04 (0.95)/1.53 (1.08)1.53 (1.17)/2.18 (1.21) 2.0-hr: 0.99 (0.71)/0.67 (0.58)/1,18 (0.93)/1.40 (1.11)/1.94 (1.18) 3.0-hr: 1.12 (0.74)/0.78 (0.67)/1.37 (0.98)/1.35 (0.98)/2.12 (1.14) 4.0-hr: 1.21 (0.82)/0.93 (0.74)/1.46 (1.04)/1.29 (0.91)/2.08 (1.08) 6.0-hr: 1.32 (0.82)/0.93 (0.82)/1.46 (0.92)/1.37 (1.01)/2.12 (0.96) 8.0-hr: 1.54 (0.98)/1.15 (0.94)/1.48 (0.94)/1.49 (1.04)/2.08 (1.05) 10.0-hr: 1.74 (1.02)/1.48 (1.01)/1.47 (0.96)/1.52 (1.06)/2.13 (0.90) 12.0-hr: 2.03 (1.00)/1.67 (0.92)/1.63 (0.96)/1.42 (1.02)/2.17 (0.96)	Small number of AE's (18) were reported. Total AE's (ER-MPH 20mg/ER-MPH 40 mg/OROS-MPH 18 mg/OROS-MPH 36 mg/placebo: 3.7%/5.6%/9.4%/11.3%/3.8% Headache: 3.7%/1.9%/1.9%/5.7%/1.9%	1 post-randomization exclusion 53/54 completed study receiving all 5 treatment conditions according to protocol	Novartis Pharmaceuticals Corporation	

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Silva 2008 US (Fair)	Male and female children ages 6-12 y who met the DSM-IV criteria for a diagnosis of ADHD were eligible. Children stabilized on a total daily dose equivalent to 40-60 mg of D,L-MPH or 20 or 30 mg/day of D-MPH for at least 2 w prior to screening were eligible.	A. Extended-release dexmethylphenidate (D-MPH ER). 20 or 30 mg/day by 2 capsules. B. D,L-MPH-ER, 36 or 54 mg/day by 2 capsules. C. Placebo by 2 capsules. Duration of study: 5 weeks	NR	Age (mean), y: 9.4 Gender, % female: 32.9 Ethnicity, %: Caucasian: 47.6 Black: 40.2 Hispanic: 8.5 Other: 3.7	DSM-IV ADHD diagnosis, %: Inattentive type: 6.1 Hyperactive-impulsive type: 0.0 Combined type: 93.9	82	3/0/79
Simpson 1980 US (Fair)	Boys aged 6-12, for whom 1) hyperactivity that had been long term; 2) complaints of hyperactivity were voiced by both the parents and teachers; 3) each child had at least average intellectual abilities as measured by the WISC-R. Subjects were evaluated for hyperactivity on the basis of a physical exam, classroom observations, and through the completion of teacher, parent, and self-ratings. Medical evaluation was designed to rule out overt brain damage or CNS trauma, cerebral palsy, convulsive disorders, CNS infection, genetic syndromes, metabolic disorders, or other medical conditions incongruous with developmental hyperactivity.	MPH, D-amphetamine, placebo for 8 weeks each	NR	Age 6-12, mean age NR 100% male Ethnicity NR	NR	12	NR/NR/12

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Silva 2008 US (Fair)	D-MPH ER vs D,L-MPH ER Changes in SKAMP-Combined score AUC 0-4 20 mg/day vs 36 mg/day: -45.35 vs -27.17, <0.001 30 mg/day vs 54 mg/day: -52.57 vs -29.28, <0.001 AUC 0-12 20 mg/day vs 36 mg/day: -113.6 vs -98.63, p-value = 0.333 30 mg/day vs 54 mg/day: -150.94 vs -107.89, p-value = 0.006 Conners' Parent Rating Scale: Change from baseline 20 mg/day vs 36 mg/day: -23.67 vs -22.52, p-value = 0.604 30 mg/day vs 54 mg/day: -22.56 vs -27.07, p-value = 0.043	D-MPH ER 20 mg/d vs D-MPH ER 30 mg/d vs D,L-MPH ER 36 mg/d vs D,L-MPH ER 54 mg/d: % of patients with AEs: 32.1 vs 26.8 vs 22.0 vs 32.9 Study-drug dosage adjustment or discontinuation: 0 Decreased appetite: 11.1 vs 2.4 vs 2.4 vs 3.8 Insomnia: 2.5 vs 1.2 vs 2.4 vs 3.8 Tics: 0 vs 2.4 vs 0 vs 1.3 Abuse potential, anxiety, and sexual dysfunction: NR	Total withdrawals: 3 Withdrawals due to TEAE/adverse event: 0	NR. 2 authors affiliated with Novartis.	
Simpson 1980 US (Fair)	Results reported only for each individual child, post-hoc analysis reported to indicate that *where a positive effect was seen* , dextroamphetamine was superior to methylphenidate - but these data are not presented.	NR	0 withdrawals; 0 withdrawals due to adverse events	NR	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Sonuga-Barke, 2009 Companion to Swanson 2004 COMACS Study	See Swanson 2004	See Swanson 2004	See Swanson 2004	See Swanson 2004	See Swanson 2004	See Swanson 2004	See Swanson 2004

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Sonuga-Barke, 2009 Companion to Swanson 2004 COMACS Study	See Swanson 2004	Barkley Stimulant Side Effect Rating Scale Effect of dose on the sleep/appetite factor scores: F[2,174]=5.12; P=0.007. The dose effect for the other factor scores (emotionality, disengaged, dizzy, uninterested, and aches) were NS. No overall effect of formulation (F[1,172]=0.01; p=0.972). Sleep problems/poor appetite were significantly worse overall on active drug vs placebo ($t^{Concerta}$ [175]=5.17; P<0.001; $t^{Equasym\ XL/Metadate\ CD}$ [173]=3.41; P=0.001). In the emotion domain, symptoms of anxiety and tearfulness improved significantly on active drug as opposed to placebo ($t^{Concerta}$ [175]=2.31; P=0.022; $t^{Equasym\ XL/Metadate\ CD}$ [173]=3.18; P=0.002). The treatment effects for the other factors were NS. The interaction between formulation and AE factor was not significant although there was trend in this direction (F[5,806]=2.83; P=0.095). Concerta vs Equasym XL/Metadate CD vs Placebo Absolute levels of AEs (cut-off score of ≥4): Insomnia and trouble sleeping: 32.37% vs 30.64% vs 21.97% Decreased appetite: 37.57% vs 31.79% vs 19.65% Irritable: 31.40% vs 30.23% vs 44.77%; P=0.001 Sad/unhappy: 16.96% vs 14.04% vs 12.87% Prone to cry: 19.08% vs 14.45% vs 21.97% Anxious: 21.39% vs 19.08% vs 34.68%; P<0.001	See Swanson 2004	See Swanson 2004	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Spencer 2011 US (Fair)	Adult outpatients with ADHD between 19 and 60 years, meeting ADHD DSM IV diagnostic criteria, receiving stable dose of IR methylphenidate for at least 4 weeks, demonstrating clinical response CGI-I of much or very much improved, were tolerant of the efficacious dose (score on the tolerability index of 0 or 1) and were satisfied with their treatment response (score of 1 or 2 on treatment satisfaction rating scale). Normal blood pressure SBP<40mmHg and DBP<90mmHg for a period of 4 weeks on a stable dose of IR Methylphenidate TID.	A. OROS Methylphenidate Mean (SD): 57.2 (26.4) B. IR Methylphenidate TID Mean (SD): 73.8 (25.2) Max dose 1.3mg/Kg/d or 144mg/d Time period: 6 weeks	NR	Mean age: 36.3 years Male:49% Ethnicity: NR	GAF score: 65.4 ADHD AISRS score: 10.8 ADHD CGI-I Very much improved: 75% Much improved: 25% Satisfaction scale Completely satisfied: 37.7% Mostly satisfied: 60.4%	53	28/0/53
Starr 2005 US Subanalysis of FOCUS	See Kemner 2005; African American group only	Mean dosages: 32.5 mg vs 1.1 mg/kg/day	See Kemner 2005	Mean age=8.8 years 82% male 100% African American	ADHD subtype Hyperactive-impulsive: 14.1% Inattentive: 9.1% Combined: 14.7% Family history of ADHD: 47% Prior treatment for ADHD: 52% Duration of ADHD: 27 months Baseline ADHD-RS: 40.6 Baseline CGI-SI: 4.9	183	NR/NR/NR

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Spencer 2011 US (Fair)	Methylphenidate IR TID vs MPH OROS (p-values are between groups) Change from baseline in ADHD AISRS rating scale (from graph): -5.2 vs-1.2, p=0.7, $F_{(1, 52)}$=0.1 % of patients satisfied with treatment(completely and mostly): 100% vs 68.3%, $x^{2:}$4.7, p=0.2 Proportion of patients who had complete compliance: 17% vs 46%, x^2=3.4, p=0.7 Mean(SD) no. of missed doses: 7.3 (6.8) vs 3.3 (4.2), F(1,51)=6.3, p=0.02 Mean change from baseline in SBP: 0.9 vs 1.7, p=0.9 Mean change from baseline in DBP: -1.5 vs 1.1, p=0.3 Mean change from baseline in pulse: 2.8 vs 4.9, p=0.1 Outliers analysis of cardiovascular data, p value between Methylphenidate IR vs OROS. SBP>140mmHg15% vs 13%, p=0.8 DBP>90mmHg8% vs 2%, p=0.3 pulse>90bpm 31% vs 30%, p=0.9	Methylphenidate IR TID vs MPH OROS (p-values are between groups) CGI Tolerability index: x^2=1.4, p=0.7 Proportion of patients reporting no adverse events: 58% vs 44% Proportion of patients reporting no interference of drug with patient functioning: 42% vs 49% Proportion of patients reporting significant interference: 0% vs 5% Proportion of patients where AE outweighed benefit: 0% vs 3%	Methylphenidate IR TID vs MPH OROS Total withdrawal: 8% vs 19.5% Withdrawals due to AE: NR vs NR	McNeil Pediatrics	
Starr 2005 US Subanalysis of FOCUS	OROS MPH vs atomoxetine: ADHD RS Total score (mean change in points): Week 1: -9.8 vs -7.5, NS Week 2: -14.5 vs -11.4; NS Week 3: -20.4 vs -15.9; p<0.03 ADHD-RS responder rates ≥ 30% reductions (% pts): 77.4% vs 61.1%; p<0.03 ≥ 50% reductions (% pts): 58.3% vs 35.2%: p<0.006 CGI-I responder rates (% pts with scores ≤2): 68.4% vs 49.1%; p<0.01 PSQ total scores: 19.8 vs 23.4; p<0.009 % parents stating that their child was doing "better than" or "somewhat better than" before treatment: 85.1% vs 63.8%; p-value NR	Treatment-related adverse events: 19.2% vs 19% Upper abdominal pain: 4.8% vs 1.7% Decreased appetite: 4% vs 1.7% Headache: 4.0% vs 1.7% Insomnia: 3.2% vs 0 Nausea: 0.8% vs 3.4% Somnolence: 0.8% vs 5.2% Sedation: 0 vs 5.2% p-values NR	Withdrawals due to adverse events: 0.8% vs 1.7%; p-value NR Overall withdrawals NR	McNeil Consumer & Specialty Pharmaceuticals	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Steele 2006 Canada (Poor)	Physically healthy, male and female outpatients, aged 6 - 12 years inclusive, with a documented Diagnostic Statistical Manual-Fourth Edition (DSM-IV) diagnosis of Attention-Deficit/Hyperactivity Disorder. These criteria were confirmed by a clinical and structured interview (the Kiddie-Schedule for Affective Disorders and Schizophrenia -Present and Lifetime Version, K-SADS-PL, version 1.0). Subjects were medication naïve or currently on ADHD medication therapy; had a baseline Clinical Global Impression-Severity (CGI-S) score of 4 or greater (at least "moderate" severity); and had to demonstrate significant after-school/evening behavioral difficulties as assessed by the clinician via parent/child interviews. To approximate clinical practice settings, psychotropic medications to treat non-ADHD disorders and psychological interventions were permitted as long as the treatment/intervention had been stable for a minimum of 4 weeks prior to entry and did not change nor newly commence during the trial.	OROS-MPH: Mean Dose: 37.8 mg/day (SD 11.9) Initiated on 18 mg once daily. Over 4 weeks, the subjects were titrated by weekly increases, at the investigators' discretion; to the next dose level (27 mg, then 36 mg) to a maximum of 54 mg. IR-MPH: Mean Dose: 33.3 mg/day (SD 13.2) Initiated at whatever dose the clinician felt was appropriate. Over 4 weeks each individual dose was titrated weekly by 5 mg or 10 mg increments, according to the manufacturer's recommendations and the investigator's clinical judgment, to a suggested maximum daily dose of 60 mg.	Psychotropic medications to treat non-ADHD disorders and psychological interventions permitted as long as treatment/intervention had been stable at least 4 weeks prior to entry and did not change nor newly commence during the trial	Mean age=9.1 yrs (Range=6-12 yrs) 83.4% male 86.9% Caucasian 3.4% black 9% other	ADHD diagnosis: predominantly inattentive=18.6% combined type=79.3% predominantly H/I=2.1%	147	2 withdrawn (didn't receive study medication) ITT n=143 Safety analysis n=145

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Steele 2006 Canada (Poor)	Achieved remission (SNAP-IV-18) at endpoint: 44% vs. 16%; p=0.0002 Remission rates higher in OROS-MPH group than in IR-MHP group at week 4 (33% vs, 14%; p=0.01) and at week 8 (47% vs. 16%; p=0.0003) <u>Mean change from baseline score (SD) at study endpoint (OROS-MPH vs. IR-MPH):</u> SNAP-IV 26-item (ADHD + ODD items) Scale: -25.5 (18.7) vs. -17.5 (15.2) SNAP-IV 18-item (ADHD items) Scale: -19.6 (13.9) vs. -14.3 (11.6) IOWA Conners Parent Rating Scale, Total: -9.4 (8.5) vs. -6.0 (5.9) IOWA Conners Parent Rating Scale, Inattention/Overactivity Sub-scale: -5.4 (4.5) vs. -3.9 (3.2) Conners Parent Rating Scale: -27.5 (21.9) vs. -19.2 (15.6) Parent Stress Index, Short Form: +14.0 (19.2) vs. +6.1 (14.8) Visual analog scale (mm): homework: -31.8 (29.6) vs. -23.0 (33.8) Visual analog scale (mm): social play: -17.9 (30.4) vs. -7.5 (27.0) CGI-I: mean rating (SD): 2.0 (1.2) vs. 2.6 (1.4); p=0.0008 CGI-S: mean change from baseline rating (SD): -2.2 (1.2) vs. -1.6 (1.4); p=0.0005 Parent satisfaction with current ADHD medication: mean rating (SD): 4.0 (1.3) vs. 3.4 (1.3); p=0.003	Adverse events were reported for 82% of subjects in both groups. No serious adverse events were reported. Any event: 82% vs. 82% Any possibly medication related event: 64% vs. 52% Decreased appetite: 24% vs. 32% Headache: 19% vs. 16% Insomnia: 17% vs. 14% Abdominal pain: 14% vs. 12% Nervousness: 13% vs. 12% Emotional lability: 13% vs. 3% Agitation: 11% vs. 7% Fatigue: 10% vs. 3% Flu-like symptoms: 10% vs. 10% Sleep disorder: 4% vs. 10%	Total =24 (16.6%) AEs=8 (5.5%)	Janssen-Ortho Inc., Canada	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Stein 2011 US NCT00393042 (Fair)	All subjects (children) met DSM-II criteria for ADHD based upon the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version.	A. Long-acting extended-release dexmethylphenidate (ER d-MPH). 10, 20, 25–30 mg B. ER mixed amphetamine salts (ER MAS). 10, 20, 25–30 mg Maximum dose was 25 mg among children <35 kg Drug dosage was titrated lowest to highest dosage in a cross-over three dose design. Duration of study: 8 weeks	NR	Age (mean), y: 11.78 Gender, % female: 27 Ethnicity, %: African American: 41 Asian: 2 Caucasian: 41 Hispanic/Latino: 7 Native American: 2 Biracial/mixed race: 7	Stimulant Use, %: No previous use: 30 Previously treated with MPH: 43 Previously treated with AMPH: 5 Previously treated with both: 22 ADHD, %: Combined type: 67 Inattentive type: 33 ADHD-RS-IV, mean (SD): 39.05 (9.74) CGI-S, mean (SD): 4.98 (0.72) CBCL internalizing, mean (SD): 58.83 (10.69) CBCL externalizing, mean (SD): 60.07 (10.41)	65	9/7/56

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Stein 2011 US NCT00393042 (Fair)	ER MAS vs ER d-MPH % of participants at highest dose rated as "much" or "very much" improved on the ADHD RS using the Reliable Change Index (RCI): 80 vs 79, p=0.855, R^2=0.00 % achieving Clinical Global Impressions-Improvement "much" or "very much" improved: 10 mg vs 20 mg vs 25 -30 mg ER MAS vs placebo: 15 vs 23 vs 25 vs 13 10 mg vs 20 mg vs 25 -30 mg ER d-MPH vs placebo: 9 vs 23 vs 24 vs 9 Dose-related decreases in Total symptom scores: p < 0.001, R^2 = 0.59 Dose-related decreases in Hyperactive-Impulsive symptom scores: p < 0.001, R^2 = 0.46 Dose-related decreases in CGI-S scores: p <0.001, R^2= 0.48 WFIRS Total Score: p = 0.008, R^2= 0.02 Family: p = 0.010, R^2= 0.02 Learning: p = 0.002, R^2= 0.03 Social Activities: p =0.018, R^2 =0.13 Risk Taking: p =0. 050, R^2=0.01	Any Adverse Event: NR SAE: 1 total (on 20 mg ER d-MPH) Withdrawals: 6 total 10 mg vs 20 mg vs 25-30 mg ER MAS vs placebo Insomnia: 7 vs 6 vs 4 vs 3 Anorexia/loss of appetite: 5 vs 7 vs 6 vs 2 Tics: 0 vs 0 vs 1 vs 0 Anxiety: 0 vs 0 vs 0 vs 0 Abuse potential, sexual dysfunction: NR 10 mg vs 20 mg vs 25-30 mg ER d-MPH vs placebo Insomnia: 2 vs 5 vs 3 vs 2 Anorexia/loss of appetite: 5 vs 7 vs 3 vs 1 Tics: 0 vs 0 vs 0 vs 0 Anxiety: 1 vs 0 vs 0 vs 0 Abuse potential, sexual dysfunction: NR	Total withdrawals: 9 Total due to TEAE/Adverse Event: 6	Novartis	

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Swanson 2004/Sonuga-Burke 2004 COMACS Study US (Fair)	Children 6-12 years old with diagnoses of a DSM-IV subtype of ADHD (inattentive type, hyperactive-impulsive type, or combined type) who were being treated with methylphenidate (MPH) 10 to 60 mg/d. Children were deemed otherwise healthy by medical history, physical examination, vital sigh measurements, and by clinical laboratory assessments. Children also had to demonstrated the ability to swallow PLA study-treatment capsules whole and without difficulty.	Methylphenidate extended release (Metadate CD®) vs methylphenidate extended release (Concerta®) vs placebo Dose level assigned according to preexisting MPH dose requirements: Low (≤ 20 mg): 20 mg vs 18 mg Medium (> 20 to 40 mg): 40 mg vs 36 mg High (> 40 mg): 60 mg vs 54 mg Duration 7 days	NR	9.6 years 73.8% male 68.9% white 11.5% black 1.7% Asian 12.4% Hispanic 5.4% other	Subtype of ADHD Inattentive: 13% Hyperactive/Inattentive: 4.8% Combined: 82.1%	184	27 (14.7%) withdrawn/lost to fu NR/184 analyzed (Metadate n=174; Concerta n=181; placebo n=183)
Taylor 2000 US (Fair)	Subjects were older than 21, and from a single local community. Subjects had to meet DSM-IV criteria for ADHD by age 7 as well as currently, with chronic course, with at least moderate impairment from the symptoms, and provide corroborating history from at least one parent or older sibling, with evidence from schoolwork or prior psychologic testing. Subjects were required to score above the 93rd percentile of symptom severity.	DAMP 10-49 mg/day in 5 mg capsules; mean dose 21.8 mg/day Modafinil 100-400 mg/day in 50 mg capsules; mean dose 206.8 mg/day Placebo (lactose) Daily dosing was on awakening and again 5 hours later. Titration occurred over 4-7 days, with fixed dose thereafter for another 7-10 days. 2-week treatment phases of placebo, modafinil, and DAMP, separated by 4-day washouts.	NR	Mean age 40.8 59% male Ethnicity NR	100% completed high school; 55% completed college 91% had family history of ADHD 73% had child or sibling with ADHD Comorbidities: 46% had at least 1 episode of depression 14% anxiety disorder and past history of alcohol dependence	22	1 withdrawn 0 lost to fu; 21 analyzed, all exposed to both DAMP & modafinil

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Swanson 2004/Sonuga-Burke 2004 COMACS Study US (Fair)	Effect sizes: Metadate CD® vs Concerta® SKAMP deportment Hours post-dose 0.0: -.23 vs -.18 1.5: 0.82 vs 0.52 3.0: 0.89 vs 0.50 4.5: 0.80 vs 0.50 6.0: 0.76 vs 0.66 7.5: 0.54 vs 0.51 12: 0.06 vs 0.25 SKAMP attention 0.0: -0.59 vs -0.58 1.5: 0.70 vs 0.41 3.0: 0.72 vs 0.48 4.5: 0.66 vs 0.42 6.0: 0.65 vs 0.64 7.5: 0.50 vs 0.53 12: 0.06 vs 0.25 PERMP - # correct math problems 0.0: -0.27 vs -0.33 1.5: 0.57 vs 0.42 3.0: 0.56 vs 0.42 4.5: 0.59 vs 0.40 6.0: 0.58 vs 0.54 7.5: 0.50 vs 0.53 12: 0.10 vs 0.28	Parent ratings of side effects on the Barkley Scale: no differences (data NR) Metadate CD® vs Concerta® vs placebo Gastrointestinal disorders: 4.6% vs 6.1% vs 7.1% Abdominal pain upper: 3.4% vs 4.4% vs 3.3% Vomiting NOS: 0.6% vs 0.6% vs 2.2% Infections and infestations: 0.6% vs 2.8% vs 1.1% Injury, poisonings, and procedural complications: 3.4% vs 1.7% vs 2.7% Metabolism and nutrition disorders: 4.6% vs 6.1% vs 2.2% Anorexia: 2.9% vs 2.8% vs 1.1% Appetite decreased NOS: 1.7% vs 3.3% vs 0.5% Nervous system disorders: 3.4% vs 5.5% vs 5.5% Headache NOS: 1.7% vs 3.9% vs 3.3% Psychiatric disorders: 6.9% vs 7.2% vs 9.3% Insomnia: 1.7% vs 1.7% vs 3.3% Irritability: 1.7% vs 1.1% vs 2.7%	Total withdrawals: NR Withdrawals due to adverse events: 0 vs 0.5% vs 1%	Celltech	
Taylor 2000 US (Fair)	Cognitive mean scores, DAMP vs modafinil: COWAT Test 86.5 vs 87.7 (ns) Digit Span forward 10.3 vs 10.3 (ns); backward 7.6 vs 7.5 (ns) Stroop Color 50.2 vs 48.0 (ns); Word 48.8 vs 48.8 (ns); Color-Word 52.0 vs 51.6 (ns) DSM-IV ADHD behavior checklist mean scores, DAMP vs modafinil: Total 20.0 vs 18.3 (ns); Hyperactivity subscore 9.0 vs 7.3 (ns); Inattention subscore 11.0 vs 10.5 (ns) Drug preference: 48% chose DAMP, 43% chose modafinil, 10% chose placebo	DAMP vs modafinil: Insomnia 38 vs 19% (ns) Irritability 14 vs 19% (ns) Muscle tension 24 vs 19% (ns) Appetite suppression 24 vs 19% (ns) Anxiety 19 vs 10% (ns) Headaches 10 vs 10% (ns) Dizziness 10 vs 0% (ns) Lingual dyskinesia 5 vs 10% (ns)	1 withdrew before receiving treatment; No withdrawals due to AEs	NR	The report provides outcomes that are the averaged data collected at baseline and at the end of each treatment phase. Data from the first phase was not made separately available.

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Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Taylor 2001 US (Fair)	Subjects were outpatient adults with ADHD (met DSM-IV criteria), with corroborating childhood history from at least one relative and examples of schoolwork and prior psychologic testing, scoring above 93rd percentile of symptom severity on both the childhood and adult versions of the ADHD Behavior Checklist.	A: DAMP maximum 20 mg/day, mean 10.2 mg/day B: Guanfacine maximum 2.0 mg/day, mean 1.10 mg/day C: Placebo 2-week treatment phases of placebo, guanfacine, and dextroamphetamine (DAMP) were separated by 4-day washouts Daily dosing was QD on awakening, beginning with 1 capsule (containing either lactose, 0.05 mg guanfacine, or 2.5 mg DAMP) and increased by an additional capsule every day to 2 days as tolerated.	NR	Mean age 41.2 41% male Ethnicity NR	100% completed high school; 23% completed college; 12% completed postgraduate degrees 70% had family history of ADHD All patients had either hyperactive or mixed subtype.	17	0/0/17

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Taylor 2001 US (Fair)	DAMP vs guanfacine: Duration of action 5.4 vs. 6.9 hours (p=0.006) Increased task motivation reported by 16 vs. 0 patients (p<0.001) Means for study measures: DSM-IV ADHD symptom total 24.2 vs 8.2 (ns); hyperactivity 10.2 vs 9.5 (ns); inattentive 14.0 vs 12.8 (ns) Copeland 66.5 vs 68.4 (ns) Beck depression 12.4 vs 12.8 (ns) Hamilton rating scale for anxiety 12.8 vs 10.8 (ns) Y-BOCS obsessions 4.5 vs 4.4 (ns); compulsions 3.7 vs 2.3 (ns) Cognitive: COWAT 79.5 vs 72.8 (ns) Stroop: Color 49.1 vs 48.8 (ns); Word 50.6 vs 51.1 (ns); Color-Word 52.4 vs 51.8 (ns); Interference 51.3 vs 50.8 (ns) Drug preference: 12 chose DAMP (citing positive effect on motivation compared with guanfacine); 4 chose guanfacine; 1 chose placebo	Muscle tension 5 (29.4%) on DAMP Fatigue 4 (23.5%) on guanfacine	0 withdrawals	NR	Data from the first phase was not reported separately. Outcomes were presented as combined data from all phases for each drug. The authors examined the effect of sequence in the crossover design, and report that no effect or interactions were found.

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Tourette's Syndrome Study Group 2002 (Fair)	Subjects aged 7-14 years, in school, and of any race or ethnic background; DSM-IV criteria for ADHD; teacher ratings of ADHD symptoms above specified cutoff scores on the IOWA CTRS (boys: grade 2-3=10, grade 4 and above=9; girls: grade 2-3=7, grade 4 and above=6); DSM-IV criteria for Tourette disorder	Mean doses: Clonidine 0.25 mg Methylphenidate 25.7 mg Combination (clonidine+methylphenidate) 0.28 mg and 26.1 mg Placebo Flexible dosing, initiated at once daily and increased to 2-3 time daily within a few days 4-week titration period, followed by 8 weeks of maintenance therapy,	Nonpharmacologic (e.g., behavioral) interventions were allowed, but remained unchanged throughout the course of the study	Mean age=10.2 85.4% male 88.3% white	100% had Tourette's syndrome Other psychiatric diagnoses: OCD: 15.8% ODD: 38.1% Conduct disorder: 9% GAD: 9.2% MDD: 5% Tic Disorder Diagnosis: Tourette syndrome: 94% Chronic motor tic disorder: 5% Chronic vocal tic disorder: 1% ADHD subtype: Inattentive: 71.3% Hyperactive/impulsive: 2.3% Combined: 26.4% Classroom observations On-task behavior: 76.7% Disruptive behavior: 10.9%	136	19/0/136
van der Meere 1999 The Netherlands (Fair)	Children, age range 7 to 12 years, all diagnosed with ADHD (DSM-III-R)	Methylphenidate 0.6 mg/kg Clonidine 4.0 mg/kg (using 25 mg Dixarit dragees) 7 weeks Twice daily dosing: Methylphenidate=breakfast/lunch; Clonidine=breakfast/evening	NR	Mean age=9.2 86.8% male Ethnicity NR	6 (11.3%) Conduct Disorder 14 (26.4%) Oppositional Defiant Disorder 2 (3.8%) Depressive/Anxiety Disorder Mean Full Scale IQ=90	53	NR/NR/53

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Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Tourette's Syndrome Study Group 2002 (Fair)	Treatment effects for clonidine vs placebo; methylphenidate vs placebo; combination therapy vs placebo (all p-values are vs placebo): ASQ-Teacher: 3.3, p=0.02; 3.3, p=0.02; 6.3, p<0.0001 ASQ-Parent: 4.7, p=0.009; 5.5, p=0.002, 5.9, p=0.002 Iowa Conners Total: 2.4, p=NS, 3.0, p=0.04; 4.8, p=0.0009 I/O: 1.7, p=0.05; 1.8, p=0.04; 3.5, p<0.0001 O/D: 0.7, p=NS; 1.2, p=NS; 1.3, p=0.05 Classroom observation On task: 4.1, p=NS; 10.2, p=0.02; 11.2, p=0.02 Disruptive: 2.3, p=NS; 1.0, p=NS; 5.1, p=NS Conners CPT Commissions: 0.8, p=NS; 2.6, p=NS; 3.2, p=NS Hit Rxn. Time: -3.8, p=NS; -4.5, p=NS; -4.4, p=NS Attentiveness: 0, p=NS; 7.0, p=NS; 9.3; p=0.02 Risk Taking: 4.8, p=NS; 9.1, p=NS; 20.6; p=0.0005 YGTSS Motor: 2.1, p=0.05; 1.3, p=NS; 2.3, p=0.03 Vocal: 2.4, p=0.05; 1.3, p=NS; 2.3, p=0.03 OI: 6.3, p=0.007; 5.8, p=0.01; 6.0, p=0.01 Total: 10.9, p=0.003; 9.4, p=0.01; 11.0, p-0.003 GTRS-parent: 3.2, p=0.02; 3.1, p=0.03; 3.5, p=0.01 GTRS-teacher: 2.1, p=NS; 1.5; p=NS; 3.2, p=0.009 TSSR-Parent Motor: 3.9, p=0.03; 3.8, p=0.04; 4.7, p=0.01 Vocal: 1.4, p=NS; 1.4, p=NS; 0.8, p=NS C-GAS: 9.0, p=0.003, 9.8, p=0.001; 14.5, p<0.0001	Clonidine vs methylphenidate Sedation (% patients): 48% vs 14%; p=0.004 Sedation (% patients rated as moderate or severe): 35% vs 8%; p=0.007	Total Withdrawals MPH=4(10.8%) Clonidine=4 (11.8%) Combination=4 (12.1%) Placebo=7 (21.9%) Withdrawals due to adverse events Combination=1 (3.4%) for ECG change; no other withdrawals due to adverse events in other groups	NR	
van der Meere 1999 The Netherlands (Fair)	Two-way MANOVA (groups, session) Mean RT: F(2, 50) - 1.83, p<0.17 Errors: F(2, 50 = 0.69, p<0.51 Contrast MANOVA analysis for each condition separately for RT MPH vs Clonidine: F(1,33) = 4.6, p<0.05 Variability of responding: F(2, 50) = 2.02, p<0.15	NR	NR NR	Sophia Foundation for Medical Research and Boehringer Ingelheim BV, the Netherlands	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Wang 2007 China, Korea and Mexico (Fair)	Patients aged 6-16 years weighing between 20 and 60 kg, who met DSM-IV criteria for ADHD, had a severity of ≥25 for boys and ≥22 for girls, or >12 for a specific subtype, on the ADHD-RS-IV-Parent Version: INV, as well as the CGI-ADHD-S. Patients were excluded if they had a history of bipolar, psychotic or pervasive development disorders; suicidal risk; ongoing use of psychoactive medications other than the study drug; those with motor tics, a diagnosis or family history of Tourette's syndrome or those who met DSM-IV criteria for anxiety disorder.	Atomoxetine Initial dose: 0.8mg/kg per day (once daily in morning) Range: 0.8-1.8mg/kg per day Methylphenidate (MPH) Initial dose: 0.2mg/kg per day (twice daily in morning and at lunch) Range: 0.2-0.6mg/kg per day	Limited OTC use	Mean age: 9.7 years 83% male 91.5% East/Southeast Asian 8.5% Hispanic	DSM-IV subtype Combined: 196 (59.4%) Inattentive: 124 (37.6%) Hyperactive/Impulsive: 10 (3%) Previous exposure to stimulants: 80 (24.2%)	330	40 withdrew 330 analyzed for safety 326 analyzed for efficacy
Weiss 2007 Canada (Fair)	Patients aged 6-17 years with DSM-IV diagnosis of ADHD, with an intelligence quotient of ≥80 on the WISC-III within the previous 12 months, score of ≥1.5 SD from norm on the Conners' ADHD index. Patients were excluded if they were allergic to MPH or amphetamines or had ah history of serous adverse reactions to MPH or had a lack of response to MPH; had a serious or unstable medical illness, co-morbid psychiatric illness of sufficient severity to require treatment, or currently receiving psychotropic medications or herbal treatments; history of drug abuse, alcohol abuse, disorder of the sensory organs, autism, psychosis, or any unstable psychiatric conditions.	MLR MPH (administered once daily) IR MPH (administered twice daily) Initial dose: 10mg for ≤20kg, 20mg for 20-35kg, 30mg for >35kg up to 40mg for ≤20kg, 50mg for 20-35kg, 60mg for <35kg	NR	Mean age: 11.0 years 82% male 83% White 6% Black 4% Asian 7% other	MPH naïve: 59%	90	11 withdrew 1 lost to follow-up 90 analyzed

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wang 2007 China, Korea and Mexico (Fair)	Atomoxetine vs MPH Completion rate: 84.1% vs 91.6% (p=0.044) Response rate: 77.4% vs 81.5% (p=0.404) ADHD-RS-IV Parent:Inv total mean change from baseline: -21.1 vs -21.6 ADHD-RS-IV Parent:Inv inattentive subscale mean change from baseline: -11.3 vs -12.0 ADHD-RS-IV Parent:Inv hyperactivity/impulsivity subscale mean change from baseline: -9.7 vs -9.5 CPRS-R:S ADHD index mean change from baseline: -11.1 vs -11.0 CPRS-R:S Cognitive problems/inattention mean change from baseline: -5.8 vs -6.0 CPRS-R:S Hyperactivity mean change from baseline: -5.9 vs -4.9 CPRS-R:S Oppositional mean change from baseline: -3.0 vs -3.4 CGI-ADHD-S mean change from baseline: -2.3 vs -2.5	Atomoxetine vs MPH Anorexia: 61 (37.2%) vs 42 (25.3%) p=0.024 Decreased appetite: 46 (28.0%) vs 32 (19.3%) Nausea: 33 (20.1%) vs 17 (10.2%) p=0.014 Somnolence: 43 (26.2%) vs 6 (3.6%) p<0.001 Headache: 25 (15.2%) vs 16 (9.6%) Dizziness: 25 (15.2%) vs 12 (7.2%) p=0.024 Abdominal pain: 15 (9.1%) vs 15 (9.0%) Pyrexia: 11 (6.7%) vs 17 (10.2%) Vomiting: 19 (11.6%) vs 6 (3.6%) p=0.007 Cough: 11 (6.7%) vs 10 (6.0%) Upper respiratory tract infection: 9 (5.5%) vs 11 (6.6%) Fatigue: 13 (7.9%) vs 5 (3.0%) Irritability: 7 (4.3%) vs 10 (6.0%) Rhinorrhea: 7 (4.3%) vs 10 (6.0%) Insomnia: 5 (3.0%) vs 9 (5.4%)	40 withdrew 24 withdrew due to AEs (18 in Atomoxetine group vs 6 in MPH group)	NR, but corresponding author is from Eli Lilly	
Weiss 2007 Canada (Fair)	MLR MPH vs IR MPH (mean questionnaire results at end of double-blind phase) CGI - therapeutic effect-investigator: 2.8 vs 2.9 CGI - adverse events-investigator: 1.6 vs 1.7 CGI - global improvement-investigator: 2.3 vs 2.3 CGI - global improvement-parent: 2.5 vs 2.6 CGI - global improvement-teacher: 2.4 vs 2.4 CPRS - ADHD index: 56.6 vs 56.8 CPRS - Cognitive/inattention: 56.7 vs 56.3 CPRS - hyperactivity: 56.9 vs 57.2 CPRS - Oppositional: 56.9 vs 56.8 CTRS - ADHD index: 56.3 vs 52.8 CTRS - Cognitive/inattention:51.8 vs 51.1 CTRS - hyperactivity: 55.4 vs 52.0 CTRS - Oppositional: 53.5 vs 51.5	MLR MPH vs IR MPH Anorexia: 20% vs 24.4% Insomnia: 20% vs 16.7% Nervousness: 17.8% vs 17.8% Headache: 13.3% vs 12.2% Somnolence: 8.9% vs 4.4% Abdominal pain: 6.7% vs 8.9% Depression: 6.7% vs 4.4% Emotional liability: 3.3% vs 6.7%	11 withdrew 4 withdrew due to AEs	Purdue Pharma	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Whitehouse 1980 US (Fair)	Children of both sexes, 6-14 years of age, with a diagnosis of minimal brain dysfunction (MBD); symptoms of MBD had been satisfactorily controlled by methylphenidate 10 mg given twice daily for at least 1 month prior to study-no medication changes were made during this period; the children were outpatients attending school, in good health, taking no other chronic medications	Standard methylphenidate 20 mg (twice daily) Sustained-release methylphenidate 20 mg (once daily) Duration=2 weeks Dosing schedule: 30 minutes prior to breakfast; 30 minutes before lunch	NR	Mean age=8.5 83.3% male 86.7% white 13.3% black	Height (inches)=50 Weight (pounds)=57.8 Right-handedness=90% Physician Questionnaire Overt Signs of Tension: 1.63 (2.00 vs 1.21; p<0.05) Teacher questionnaire Tension/Anxiety: 10.9 (10.00 vs 12.00; p<0.05)	34	4 (11.8%) withdrawn/0 lost to fu/30 analyzed
Wigal 2005 StART study US (Fair)	Male or female aged 6 to 12 years; diagnosis of DSM-IV-TR ADHD combined subtype or predominantly hyperactive/impulsive subtype; weight between 40 lb and 120 lb at enrollment; and capable of understanding and following classroom instruction and generally functioning academically at age-appropriate levels	Atomoxetine: wk1=0.5 mg/kg/d; wk2-3=1.2 mg/kg/d Mixed amphetamine salts (MAS) XR: wk1=10 mg; wk2=20 mg; wk3=30 mg (mean dosages NR) Duration=3 weeks (wk)	NR	Mean age=8.7 years 71.9% male 55.6% white 16.2% black 19.7% Hispanic 2.0% Asian or pacific islander 6.4% other	ADHD subtype Hyperactive/impulsive: 0.5% Combined: 99.5% CGI-S category: Borderline impairment: 2.5% Mildly impaired: 3.9% Moderately impaired: 60.1% Markedly impaired: 25.6% Severely impaired: 9.3%	215	25 (12.3%) withdrawn/lost to FU NR/203 (94.4%) (MAS XR n=102; atomoxetine n=101)

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Whitehouse 1980 US (Fair)	Mean change scores (visit 3 compared to visit 1) for sustained release vs standard: Teacher Total score: -1 vs -8, p<0.05 Conduct Problem: 0 vs -3, p<0.05 Inattentive/Passive: 0 vs 0 Tension/Anxiety: -1 vs -1 Hyperactivity: 0 vs -2 Social ability: 0 vs 0 Parent/teacher questionnaire: 0 vs -1 Parent Questionnaire Total score: -11 vs -8 Conduct Problem: -2 vs 0; p<0.05 Anxiety: -1 vs -2 Impulsive/Hyperactive: -2 vs 0 Learning problem: 0 vs 0 Psychosomatic: -1 vs 0 Perfectionism: 0 vs 0 Antisocial: 0 vs 0 Muscular tension: -1 vs 0 Parent/Teacher Questionnaire: -2 vs -1	Adverse reactions: 5 (31.3%) vs 2 (14.3%), p=NS (consisted of headache, hyperactivity and restlessness)	4 (11.8%) (group assignment NR) No withdrawals due to adverse events	NR	
Wigal 2005 StART study US (Fair)	MAS XR vs atomoxetine SKAMP scale mean changes Deportment: -0.56 vs -0.13; p<0.0001 Attention: -0.49 vs -0.08; p<0.0001 SKAMP scale responders Deportment (≥ 25% improvement): 70% vs 38%; p≤0.0001 Attention (≥ 25% improvement): 68% vs 28%; p<0.0001 Math problems (mean number) Attempted: 62.6 vs 30.5; p<0.0001 Completed correctly: 61.6 vs 29.0; p<0.0001 CGIS-P mean decrease in unit points: -8.3 vs -6.63; p=NS CGI-I ratings of very much improved/much improved (% pts): 74.5% vs 35.6%; p<0.0001 PedsQL total score mean increase in unit points: +7.1 vs +7.9; p=NS PedsQL school functioning score increase in unit points (% increase): +34% vs +25%; p=0.0026 Parent-Rated Med-SS: MAS XR=atomoxetine (data NR)	MAS XR vs atomoxetine (p-values NR for all; those reported below reflect Oregon EPC calculations using StatsDirect) Overall AE incidence: 85% vs 73.1%; NS Upper abdominal pain: 18.7% vs 14.8% Vomiting: 4.7% vs 13%; p=0.035 Fatigue: 1.9% vs 7.4% Nausea: 6.5% vs 9.3% Weight decrease: 5.6% vs 3.7% Anorexia: 16.8% vs 9.3% Appetite decrease: 28% vs 17.6% Dizziness: 5.6% vs 1.9% Headache: 15% vs 10.2% Somnolence: 4.7% vs 18.5%; p=0.0015 Insomnia: 28% vs 7.4%; p<0.0001	Overall withdrawals: 13.1% vs 10.2%; NS AE withdrawals: 6.5% vs 3.7%; NS	In part by NIMH award MH02042 and a grant from Shire	

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/ analyzed
Wolraich 2001 US (Fair)	Boys and girls, ages 6 to 12 years, with a clinical diagnosis of any subtype of ADHD; patients who were taking MPH or had taken it in the past had to have been on a total daily MPH dose (IR or IR/SR combination) of at least 10 mg but not more than 60 mg)	Methylphenidate (MPH) mean dose=29.5 (three times daily at 7:30, 11:30 and 3:30) Methylphenidate osmotic, controlled-release, oral dosage form (OROS MPH) mean dose=34.3 (once daily at 7:30) Duration=4 weeks Patients that had not been receiving MPH during 4 weeks prior to study entry started in a 4-week open titration phase where they were ALL given OROS MPH at 18 mg QD and this was increased to 36 mg QD and then to 54 mg QD as necessary	NR	Mean age=9 82.6% male 84.4% White 7.4% Black 0.4% Asian 3.5% Hispanic	ADHD Diagnosis 73.4% combined 19.5% inattentive 7.1% hyperactive/impulsive Previous stimulant therapy 20.2% None 6.4% Not in previous 4 weeks 5.7% Non-MPH 67.7% MPH	312	Withdrawn=206 (66%)/Lost to follow-up=1(0.3%)/Analyzed=277 (MPH n=94, MPH OROS n=94, Placebo n=89)

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Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial Name (Quality)	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wolraich 2001 US (Fair)	Mean change in IOWA Conners Scores (OROS MPH vs IR MPH) (p-values NR, but narrative states there are NS differences): Teacher/Parent scores: Inattention/Overactivity: -3.76/-4.79 vs -3.59/-3.73 Oppositional/Defiance: -1.6/-3.24 vs -1.3/-2.36 Mean changes in secondary measures of efficacy (teacher ratings) Peer Interaction: -0.33 vs -0.21 SNAP-IV Inattention: -0.69 vs -0.80 SNAP-IV Hyperactivity/Impulsivity: -0.64 vs -0.69 SNAP-IV Oppositional Defiant Disorder: -0.36 vs -0.32 Global Efficacy at end of study: 1.42 vs 1.43 Mean change in secondary measures of efficacy (parent ratings) SNAP-IV Inattention: -0.91 vs -0.77 SNAP-IV Hyperactive/Impulsive: -0.91 vs -0.74 SNAP-IV Oppositional Defiance Disorder: -0.65 vs -0.41 Global Efficacy at end of study: 1.47 vs 1.28 Investigator ratings Mean CGI at end of study: 4.24 vs 4.19 % of patients on CGI rated as "much" or "very much" improved: 46.7% vs 47.2% Other Global assessment of efficacy, % patients teachers/parents rated as "good or excellent": 42.9%/54.0% vs 46.9%/46.5% CGI, % patients rated as "very much improved or much improved": 46.7% vs 47.2% Parent Satisfaction Questionnaire (% pleased/very pleased/extremely pleased): 62.6% vs 64%	Any adverse event: 42.3% vs 46.2%, p-value NR Sleep: no differences (data NR) Appetite (% of patients who were eating less than usual during the previous two weeks): day 14=22.5% vs 18.8%, p=NS; day 28=data NR but described as "similar" New onset tics (# patients): 0 vs 1 (1%), p=NS	Withdrawals due to adverse events: 1% vs 1% Total withdrawals: 15 (16%) vs 13 (13.8%)	Alza	Although the numbers enrolled vs analyzed are described in the text and in a figure, they are confusing and difficult to reconcile with each other.

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
Adler 2011	Unclear	Unclear	Unclear; crossover and did not present data for first period	Yes	Yes	No; open	No; open	No; excluded 21%, only completers
Amiri 2008	Yes	Yes	Unclear (inadequate data presented)	Yes	Yes	Yes	Yes	Yes
Arnold 1978 Huestis 1975	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes
Barkley 2000	NR	NR	Crossover	Yes	Yes	Yes	Yes	No
Bédard 2015	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No
Bergman 1991	Inadequate (counterbalanced order)	NR	N/A - crossover	No	Yes	Yes	Yes	Unclear
Biederman 2007 Lopez 2011	Randomization stated, but method NR	Unclear	Yes	Yes	Unclear; "double-blind" stated	Unclear; "double-blind" stated	Yes	Yes
Borcherding 1990	NR	NR	Crossover	Yes	Yes	Yes	Yes	No
Castellanos 1997	NR	NR	Crossover	Yes	Yes	Yes	Yes	No
Coghill 2013 Banaschewski 2013 Soutullo 2013 Coghill 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
Adler 2011	*Not rated*	*Not rated*	*Not rated*	*Not rated*	*Not rated*	No (21%); Yes	Fair
Amiri 2008	No	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Fair
Arnold 1978 Huestis 1975	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Barkley 2000	1 excluded due to low IQ	*Not rated*	NR	Reported that 20 - 31% completed each randomized order of drug administration	*Not rated*	*Not rated*	Poor
Bédard 2015	*Not rated*	*NA*	*Not rated*	*Not rated*	*NA*	*Yes, Yes*	Fair
Bergman 1991	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Biederman 2007 Lopez 2011	No	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Fair
Borcherding 1990	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Castellanos 1997	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Coghill 2013 Banaschewski 2013 Soutullo 2013 Coghill 2014	*Not rated*	*NA*	*Not rated*	*Not rated*	*NA*	*No (42%), No (62% in placebo, 30% LDX, 34% MPH OROS)*	Fair

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
Connor 2000	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes
Connor 2000	Unclear; 3 subjects refused MPH alone and were "partially randomized" to other arms.	Unclear, no details	Unclear; The Total Teacher CBCL was 4.9 points different between monotherapy groups.	Yes	Yes for teachers and research assistants; probably not for parents due to EKGs only in clonidine groups	Probably not due to EKGs only in clonidine groups	Probably not due to EKGs only in clonidine groups	Unclear; 3/25 (12.5%) non-completers, but no details about how handled in analyses
Cox 2004	Yes, random numbers table	NR; Use of a random number table without a 3rd party may indicate lack of allocation concealment	N/A - crossover	Yes	Unclear (abstract states study was single-blind, no other details)	Unclear (abstract states study was single-blind, no other details)	Unclear (abstract states study was single-blind, no other details)	No
Dittmann 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Efron 1997	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes
Efron 1998	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes
Elia 1990	NR	NR	Crossover	Yes	Yes	Yes	Yes	Unclear
Elia 1991	NR	NR	Crossover	Yes	Yes	Yes	Yes	Unclear

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
Connor 2000	No	*Not rated*	No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Connor 2000	*Not rated*	Unclear; 12.5% non-completers but no details about N analyzed	*Not rated*	*Not rated*	Unclear, "all subjects were acceptably compliant", unclear	Yes, No (MPH only=12.5%, clonidine only=25%)	Poor
Cox 2004	No	*Not rated*	No/No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Dittmann 2013	*Not rated*	*NA*	*Not rated*	*Not rated*	*NA*	*No (23% overall), Yes (equal between groups)*	Fair
Efron 1997	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Efron 1998	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Elia 1990	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Elia 1991	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
Elia 1993	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes
Findling 2006	Unclear; randomized in a ratio of 3:3:1 (p 452)	NR	Yes, for treatment arms; O/D component of IOWA Conners' Scale lower (better) in placebo group compared to either treatment group	Yes	NR	Yes	Yes	Yes; stated in results, no data provided
Findling 2008	Yes	Unclear	Mostly, except for prior ADHD medication use, which was slightly higher in the MTS group	Yes	Yes	Yes	Yes	Not true ITT but small # not included. However, numbers in text and on figure disagree on how many not included.
Fitzpatrick 1992	Unclear. No use of "randomized" terminology; No description whatsoever of group assignment	NR	N/A - crossover	No	Yes	Yes	Yes	Unclear
Garg 2014	Yes	Unclear	Some differences; more Inattentive in MPH group and more with ODD in Atomox group	Yes	No	No	No	No

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
Elia 1993	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Findling 2006	Yes; 6 based on clinician's judgment (5 in placebo; 1 in MPH-IR)	*Not rated*	No/No; Placebo group had a high % of study withdrawal compared to the two treatment arms; withdrawal data on page 454.	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Findling 2008	Several patients withdrew after being randomized, but prior to having at least 1 primary efficacy assessment (planned for 1 week after dose optimization) = 3-4% of total. Not reported which groups these had been randomized to.	*Not rated*	Yes (62% of placebo group withdrew compared to 27.5% in both MTS group and MOS group) Yes (all groups >20% withdrew)	Yes/NR	*Not rated*	*Not rated*	Fair/Poor
Fitzpatrick 1992	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Garg 2014	*Not rated*	*NA*	*Not rated*	*Not rated*	*NA*	*30% for efficacy, 21% for adverse effects*	Poor

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Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
Gau 2006	NR	NR	Yes	Yes	Partial; parent reporters knew which medication, teachers reporters did not	NR	No	Yes
Gross 1976	NR	NR	Crossover	Yes	Yes	Yes	Yes	No
Hervas 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
James 2001	NR - order of dose random, but order of drug not clear	NR	N/A - crossover	Yes	Unclear - dose of DEX SR increased part way through study	Yes	Yes	Yes for some efficacy measures; No for CPS and side effects
Kauffman 1981	NR	Yes	Crossover	Yes	Yes	Yes	Yes	Yes
Kemner 2005	NR	NR	No; OROS patients with greater severity of illness at baseline (ADHD-RS 39.9 vs 38.6; p=0.006); adjusted for this difference in the analysis	Yes	NR	No	No	NR

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
Gau 2006	No	*Not rated*	No/No	Yes Yes Yes No IR MPH group had less adherence than the OROS MPH group (p < 0.0001); report states this did not change the results	*Not rated*	*Not rated*	Fair
Gross 1976	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Hervas 2014	*Not rated*	*NA*	*Not rated*	*Not rated*	*NA*	*Yes, Yes*	Good
James 2001	No	*Not rated*	NR/NR	Yes NR NR NR	*Not rated*	*Not rated*	Poor
Kauffman 1981	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Kemner 2005	NR	*Not rated*	NR	NR Yes NR NR	*Not rated*	*Not rated*	Poor

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
Kratochvil 2002	NR	NR	Yes	Yes	Yes	Yes	Yes	No; 10 (4.4%) excluded from analysis due to not having a post-baseline visit
Kuperman 2001	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported	Yes	No: 81.1%
Lopez 2003	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	Yes
Manos 1999	No, each child's pediatrician determined whether MPH or Adderall was to be used (based on familiarity, as well as whether they wanted a child to receive a single dose or twice-daily dose)	NR	Yes	Yes	No	No	No	Yes
McCracken 2003	Unclear; Latin square design;	Yes; randomization schedules generated by the sponsor and distributed to the onsite pharmacist	N/A - crossover	Yes	Yes; states double blind but no details	Yes; states double blind but no details	Yes; states double blind but no details	Yes

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Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
Kratochvil 2002	No	*Not rated*	No/No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Kuperman 2001	No	*Not rated*	No/No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Lopez 2003	No	*Not rated*	None	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Manos 1999	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
McCracken 2003	No	*Not rated*	No/No	Yes Yes Yes No	*Not rated*	*Not rated*	Fair

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Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
Muniz 2008	Yes	Yes	NR (only means for whole group given, not separated by group to see how they compare)	Yes	Unclear - "double blind"	Yes	Yes	Yes
Newcorn 2008	Randomization stated, but method NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Palumbo 2008	Yes	Yes	Unclear; clonidine group had highest proportions of whites, family history of ADHD, and prior stimulant treatment	Yes	Yes	Yes	Yes	Yes
Pelham 1987	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	Unclear
Pelham 1990	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	Unclear
Pelham 1999a	NR	NR	Crossover	Yes	Yes	Yes	Yes	Unclear
Pelham 1999b	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes
Pelham 2001	Yes	Yes for patients	N/A - crossover	Yes	Yes	Yes	Yes	No; 2 patients excluded (2.8%)

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Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
Muniz 2008	No	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Fair
Newcorn 2008	No	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Good/Fair
Palumbo 2008	*Not rated*	Yes	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Overall=No (36%) Between-groups=No (placebo=67%, MPH=38%, clonidine=16%, combination=25%)	Fair
Pelham 1987	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Pelham 1990	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Pelham 1999a	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Pelham 1999b	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Pelham 2001	No	*Not rated*	NR/NR	Yes, NR, Yes (virtually 100%), NR	*Not rated*	*Not rated*	Fair

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
Pelham 2011	Unclear	Unclear	Unclear, no comparison based on order of randomization (crossover trial)	Yes	Unclear	Yes, double-dummy	Yes, double-dummy	No; exclusion of 1/10 (10%) of patients
Pliszka 2000 Faraone 2001	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes
Prasad 2007	NR	NR	No, higher proportion with inattentive subtype in Atomoxetine group (11.5%) vs control (3.1%)	Yes	No	No	No	Unclear - modified ITT stated, appears only 75% of atomoxetine group included in analysis, while 94% of control group
Sangal 2006	NR	NR	N/A - crossover; reported no differences at baseline	Yes	Yes; states double blind but no details	Yes; states double blind but no details	Yes; states double blind but no details	No
Schachar 2008	Yes	Yes	NR	Yes	Unclear - "double blind"	Unclear - "double blind"	Yes	Yes
Sharp 1999	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes

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Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
Pelham 2011	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Yes; Yes	Fair
Pliszka 2000 Faraone 2001	No	*Not rated*	No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Prasad 2007	Yes; No	*Not rated*	Yes (discontinuation from trial 25% atomoxetine, 6% control No	Yes NR NR NR	*Not rated*	*Not rated*	Poor
Sangal 2006	Yes; 35 due to low actigraphy scores or equipment malfunction	*Not rated*	No/No	Yes Yes Yes No	*Not rated*	*Not rated*	Poor
Schachar 2008	No	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Fair
Sharp 1999	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
Silva 2005	Unclear; For counterbalancing, 10 crossover treatment sequences used; Williams design to control for effects of treatment order and relative position.	NR	NR; only data on entire study group	Yes	Yes	No; those dispensing medication not blinded	Yes; although states some might have known what they were taking	Unclear
Silva 2008	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No - required both one dose and one post0dose efficacy measurement.
Simpson 1980	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	Yes
Spencer 2011	Unclear	Yes, "…by the MGH Research Pharmacy"	Unclear; in OROS group, fewer were completely satisfied (33% vs 58%) and more had no adverse events (51% vs 33%)	Yes	Yes for efficacy, no for adverse events	Unclear, described as single-blind, but no information about capsule appearance and how concealed multiple daily dosage regimen from single daily dosage regimen	Same as care provider	Yes

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Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
Silva 2005	No	*Not rated*	No/No	No No No No	*Not rated*	*Not rated*	Fair
Silva 2008	*Not rated*	*NA*	*Not rated*	*Not rated*	*NA*	*Yes, Yes*	Fair
Simpson 1980	No	*Not rated*	No	NR NR NR NR	*Not rated*	*Not rated*	Fair
Spencer 2011	*Not rated*	Unclear, reasons for noncompletion NR	*Not rated*	*Not rated*	Unclear, no for OROS-MPH group (complete compliance=46%), unclear	Yes, No (IR-MPH=8%, OROS-MPH=20%)	Fair

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
Steele 2006	Yes; Site randomization lists	Yes	Yes	Yes	No	No	Yes	Yes
Stein 2011	Unclear	Unclear	Unclear. Higher % with no prior stimulant use in those not completing the crossover.	Yes	Yes	Yes	Yes	No
Swanson 2004	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	Yes
Taylor 2001	Unclear	Unclear	Unclear; no comparison of characteristics based on order of randomization to crossover design	Yes	Unclear; unmarked capsules used, but use of crossover design and once daily dosing of short-acting drugs may have increased risk of detecting drug assignment	Unclear; unmarked capsules used, but use of crossover design and once daily dosing of short-acting drugs may have increased risk of detecting drug assignment	Unclear; unmarked capsules used, but use of crossover design and once daily dosing of short-acting drugs may have increased risk of detecting drug assignment	Yes (df=16 for ANOVA in Table 1)
Taylor 2000	Method not reported	Method not reported	Not reported	Yes	Yes but method not described	Not reported	Yes	No: 95.4%

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Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
Steele 2006	NR	*Not rated*	No/No	Yes/NR/Y/NR % of subjects who missed any dose during the trial was higher with IR-MPH (84%) than OROS-MPH (56%).	*Not rated*	*Not rated*	Poor
Stein 2011	*Not rated*	*NA*	*Not rated*	*Not rated*	*NA*	*Yes, unclear*	Fair
Swanson 2004	No	*Not rated*	NR/NR	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Taylor 2001	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Unclear, Unclear	Fair
Taylor 2000	No	*Not rated*	No/ no	Yes NR NR NR	*Not rated*	*Not rated*	Fair

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Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
Taylor 2001	Method not reported	Method not reported	Not reported	Yes	Yes but method not described	Not reported	Yes	Yes
Tourette's Syndrome Study Group 2002	Yes	Yes	No, MPH group had higher age (10.7 vs 9.7 yrs) and maturity (19% vs 9% pubescent), fewer children with inattentive subtype (65% vs 76%) and lower Conners ASQ-Teacher score (13.2 vs 16.4)	Yes	Yes double dummy assessors were parents and teachers	Yes, double-dummy	Yes, double-dummy	Yes, LOCF
Tourette's Syndrome Study Group 2002	Yes, computer-generated randomization	Yes, central coordinating center	No, differences in age, proportions of ADHD subtype, ASQ-Teacher scores, and gender	Yes	Yes	Yes	Yes	Yes
van der Meere 1999	Unclear	Unclear	Unclear; fewer boys in placebo group (placebo=66%, MPH=94%, clonidine=100%); very few baseline characteristics reported (sex, age, IQ)	Yes	Yes, explicit statement	Yes, explicit statement	Yes, explicit statement	Yes

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Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
Taylor 2001	No	*Not rated*	No/ no	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Tourette's Syndrome Study Group 2002	*Not rated*	Yes	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Yes (14%); Yes across treatment groups (range, 11% to 12%), but higher in placebo group (22%)	Fair
Tourette's Syndrome Study Group 2002	No	*Not rated*	No/No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
van der Meere 1999	*Not rated*	Yes	*Not rated*	*Not rated*	Yes, Unclear, Unclear	No attrition	Fair

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Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat analysis
van der Meere 1999	NR	NR	Boys and girls were not equally distributed among the groups	No	Yes	Yes	Yes	Yes
Wang 2007	Randomization stated, but method NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Weiss 2007	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes
Whitehouse 1980	NR	NR	No, SR/IR on Overt signs of tension and IR>SR on tension/Anxiety	Yes	Yes	Yes	Yes	No, 4 (11.8%) excluded from analysis; not stated which groups these 4 were assigned to
Wigal 2005	NR	NR	Yes	Yes	Yes	Yes	Yes	No; 12 (5.6%) excluded from analysis; reasons for exclusion unclear
Wolraich 2001	Yes	Yes	Small differences (NS): proportions with comorbidities, prior MPH IR use, inattentive vs combined ADHD	Yes	Yes	Yes	Yes	Yes

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Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 5)*	Quality Rating
van der Meere 1999	No	*Not rated*	NR/NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Wang 2007	NR	*Not rated*	No/Yes MPH group had more complete than atomoxetine group (91.6% vs 84.1%; p=0.044)	Y/NR	*Not rated*	*Not rated*	Fair
Weiss 2007	NR	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Fair
Whitehouse 1980	Yes, 4 excluded from analysis for: 2 dosage deviations, 1 viral illness, 1 "other reasons"	*Not rated*	None/None	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Wigal 2005	NR	*Not rated*	None	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Wolraich 2001	No	*Not rated*	No/No	Yes NR NR NR	*Not rated*	*Not rated*	Fair

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Barbaresi 2007 (Fair)	Retrospective, population-based cohort	Any stimulants Duration: Followed from age 5 until emigration, death, school graduation, or dropout. Median age at last follow-up was 18.4 years	Cumulative school records for every child born in Rochester, MN between January 1, 1976 and December 31, 1982 to mothers residing in Independent School District	370
Charach 2006 (Poor)	Open-label extension study	Psychostimulants (% patients): 43 (54%) DEX: 19% MPH: 81% Dosages NR Duration: 5 years	Children who had completed a 12-month randomized-controlled trial of combined MPH and parent-treatment groups; original trial began in 1993	79

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Barbaresi 2007 (Fair)	Median age at last follow-up: 18.4 years 74.9% male Ethnicity NR	**Academic achievement** Stimulant yes/no: P = 0.75 Average daily dose: P = .058 Duration of treatment with stimulants, yr: P= 0.32 Age at onset of treatment with stimulants, yr: P = 0 .66 Type of educational intervention: P < 0.001 Maternal education at birth: P < 0.001 **Percentage of days absent by grade level** Stimulant yes/no: P=0.012 Average daily dose: P=0.71 Duration of treatment with stimulants, yr: P=0.041 Age at onset of treatment with stimulants, yr: P=0.34 Comorbid conditions: P=0.006 Type of educational intervention: P<0.001 Maternal education at birth: P=0.005 **Grade retention** Type of educational intervention: P<0.001 Maternal education at birth: P<0.001 **Dropping out of school** Stimulant yes/no: P=0.54 Average daily dose: P=0.35 Duration of treatment with stimulants, yr: P=0.52 Age at onset of treatment with stimulants, yr: P=0.54 Comorbid conditions: P=0.003 Type of educational intervention: P<0.001 Maternal education at birth: p<0.001
Charach 2006 (Poor)	NR	NR

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Author, year Country	Harms	Funder	Comments
Barbaresi 2007 (Fair)	NR	Public Health Service, National Institutes of Health (HD29745 and AR30582) and McNeil Consumer and Specialty Pharmaceuticals	
Charach 2006 (Poor)	Association between increased dose and height (controlled for time since initiation of treatment): ß coefficient = -0.11, p<0.001 Association between increased dose and weight (controlled for time since initiation of treatment): ß coefficient = -0.29, p<0.001	National Health Research Development Program of Canada, and the Department of Psychiatry of the Hospital for Sick Children, Toronto, Ontario, Canada	

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Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Charles 1981 (Fair/Poor)	Cross-sectional	Group 1: Stimulants < 6 months Group 2: Stimulants 6 mos to 2 years Group 3: Stimulants 2-3 years Group 4: Stimulants 3-4 years, but had discontinued ≥ 1 month prior to follow-up Group 5: Still on stimulants (MPH or pemoline) Duration: 4 years	Setting: UCLA Department of Pediatrics	62
Garnier 2010 U.S. (Poor)	Cross sectional	Amphetamine/DEX, MPH, MPH extended release, other; dosages not reported Duration: Not reported, "current use"	Time Frame: August 2006 to August 2007 Data source: Survey of college students from a large public university in the mid-Atlantic region of the United States. Data from third annual interview of cohort participating in prospective, longitudinal study of health behaviors	Overall=483 Prescribed ADHD medication=81 Amphetamine or DEX=44 MPH=27 MPH extended release=23 Other=11

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Charles 1981 (Fair/Poor)	Mean age=12 years, 3 months 79% male 88.7% white 9.7% black 1.6% Hispanic	Group 1 vs 2 vs 3 vs 4 vs 5 <u>Teacher reports of below grade level work (% children):</u> Reading: 77 vs 75 vs 64 vs 73 vs 83 Spelling: 69 vs 75 vs 64 vs 55 vs 75 Mathematics: 69 vs 100 vs 56 vs 73 vs 58 Ability to sustain attention: 38 vs 75 vs 71 vs 73 vs 75 Unclear oral language: 15 vs 12 vs 14 vs 45 vs 50 <u>Other</u> Percentage of repeated grades (%): 46 vs 50 vs 36 vs 31 vs 8 Special education class placement: 31 vs 60 vs 36 vs 31 vs 58 Currently tutored: 15 vs 30 vs 14 vs 23 vs 41
Garnier 2010 U.S. (Poor)	Overall: 46% male 77% white Mean age not reported (range, 17 to 19 years) 46% met criteria for alcohol use disorder in past year 19.7% ever diagnosed with ADHD Characteristics for subgroup prescribed ADHD medication not reported	NR

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Charles 1981 (Fair/Poor)	NR		
Garnier 2010 U.S. (Poor)	Individuals who diverted medication: Amphetamine or DEX=70.5% MPH=37.0% MPH extended release=39.1% Other=27.3% For overall group, multivariate analyses found 'number of prescription drugs used nonmedically in the past year' and 'childhood conduct problems' to be significantly associated with diversion, independent of demographics and other risk factors. Correlates of diversion not investigated for ADHD drug subgroup.	National Institute on Drug Abuse, National Institutes of Health and an investigator-initiated award from Ortho-McNeil-Janssen	

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Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Germinario 2013 Italy (Poor)	Prospective observational study	A. Methylphenidate (MPH) [10 mg tablet, 0.3–0.6 mg/kg/dose/day, bid or tid] B. Atomoxetine (ATX) [5 mg, 10 mg, 18 mg, 25 mg, 40 mg, or 60 mg tablets, 0.5-1.2 mg/kg/day, QD] Duration of exposure: 24 months.	Time frame: June 2007 to June 2010. Data source: 87 centers accredited for the management of ADHD	1758
Goldman 2008 U.S. (Fair/Poor)	Case control	MPH DEX Combined DEX and amphetamine Duration: 5 years	All patients with symptoms of cold hands and feet seen at the rheumatology clinic of Akron Children's Hospital and Medical Center between January 2001 and December 2005 underwent pulse volume recording with ice water exposure at a vascular laboratory. The charts of these patients were reviewed for the present study.	64

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Germinario 2013 Italy (Poor)	Included in the weight analysis 590 subjects vs height analysis 574 subjects, %: <11 years: 57.8 vs 59.3 11-<15 years: 35.1 vs 34.8 ≥ 15 years: 7.1 vs 5.9 % female: 12.9 vs 12.9 Type of ADHD, ADHD-I: 5.6 vs 5.7 ADHD-H: 4.4 vs 4.7 ADHD-C: 90.0 vs 89.6 Comorbidity, Oppositional defiant disorder: 41.9 vs 42.3 Conduct disorder: 5.4 vs 5.7 Depression: 5.4 vs 5.7 Anxiety: 12.4 vs 12.0 Learning disorder: 45.6 vs 46.2	NR
Goldman 2008 U.S. (Fair/Poor)	Mean age cases: 15.9 years controls: 16.1 years 28.2% males Ethnicity: NR	NR

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Germinario 2013 Italy (Poor)	MPH vs ATX: Weight Analysis: **0 to 12 months** percentile, %: Decreased: 31.5 vs 45.9 Unchanged: 50.0 vs 36.6 Increased: 18.5 vs 14.5 MPH vs. ATX X^2 = 7.48, p = 0.024 **0 to 24 months** percentile, %: Decreased: 41.8 vs 53.6 Unchanged: 30.9 vs 32.1 Increased: 27.3 vs 14.3 MPH vs. ATX X^2 = 1.94, p = 0.380 Height Analysis: **0 to 12 months** percentile, %: Decreased: 27.5 vs 34.5 Unchanged: 54.5 vs 54.0 Increased: 18.0 vs 11.5 MPH vs. ATX X^2 = 3.31, p = 0.191 **0 to 24 months** percentile, %: Decreased: 30.9 vs 40.0 Unchanged: 45.5 vs 45.7 Increased: 23.6 vs 14.3 MPH vs. ATX X^2 = 1.45, p = 0.485 Other harms of interest: NR	Italian Medicine Agency (AIFA)	
Goldman 2008 U.S. (Fair/Poor)	McNemar's test showed a significant association between past or current use of ADHD stimulants and the presence of RS (x^2=5.00, P=0.01) Controls had significantly higher CRP levels compared to cases (P=0.03) Controls had significantly higher ESR levels compared to cases (P<0.001)	NR	

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Gross 1976 U.S. (Fair)	Retrospective analysis of height and weight data among 100 children treated for at least 2 years for ADHD, and with mean follow-up of 6 years. Comparative	MPH mean dose 34 mg/day, n=60 DEX mean dose 16.5 mg/day, n=24 (Imipramine/desipramine, n=16) Subjects received at least 2 (mean=5) years of treatment. Mean follow-up time: 5.8 years for MPH, 6.8 years for DEX.	All the weight and height data the researchers were able to accumulate from past records of children they had been treating, as well as measurements made in their office. Time frame NR.	100

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Gross 1976 U.S. (Fair)	Mean age at onset of treatment: 9 Gender 82% Ethnicity NR At final measurement, 45% were aged 16+ 17% were aged 18+	NR

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Gross 1976 U.S. (Fair)	Average in percentile of weight, MPH vs DEX: Time after onset: 1 year, -5.2 (p<0.05) vs -5.9 (NS); 2 year, -4.3 (NS) vs -6.0 (NS); 3 year: -3.0 (NS) vs -3.4 (NS)	NR	Loss of weight compared with expected norms occurs during the first 3 years with MPH and DEX, but there is a statistically significant increase in weight and height percentiles at final measurement in both treatment groups. Compliance was assessed by checking prescription records.

Methylphenidate group: changes in percentiles of weight and height				
Time after onset (yrs)	N on medication	Mean daily dose	Average change in percentile (p-value)	
			Weight	Height
1	60	24.4	-5.2 (p<0.05)	-0.1 (ns)
2	60	31.7	-4.3 (ns)	+0.4 (ns)
3	54	38.5	-3.0 (ns)	-1.9 (ns)
4	44	43.3	+7.5 (ns)	+7.0 (ns)
5	35	47.2	+7.2 (ns)	+7.1 (ns)
6	24	51.2	+10.4 (ns)	+8.9 (ns)
7	15	40.0	+24.4 (p<0.05)	+14.9 (p<0.05)
8	6	40.0	+19.1 (p<0.05)	+12.2 (p<0.05)
At final f/u (mean 5.8y)	30	43.8	+11.4 (p<0.001)	+12.8 (p<0.001)
Dextroamphetamine group: changes in percentiles of weight and height				
1	24	12.2	-5.9 (p<0.05)	-1.8 (ns)
2	24	14.5	-6.0 (ns)	+0.8 (ns)
3	24	17.7	-3.4 (ns)	+1.9 (ns)
4	22	18.9	+2.2 (ns)	+5.2 (ns)
5	15	20.1	+3.2 (ns)	+6.2 (ns)
6	12	16.7	+9.3 (ns)	+9.8 (ns)
7	6	18.0	+18.1 (ns)	+13.4 (ns)
8	4	20.0	+10.5 (ns)	+13.2 (ns)
9	2	25.0	+41.0 (ns)	+17.3 (ns)
At final f/u (mean 6.8y)	12	19.6	+16.0 (p<0.02)	+10.9 (p<0.01)

Patients who had discontinued medication at final follow-up had larger increments in percentiles for both height and weight compared with patients still taking medication, but differences were not significant.
Analysis by age at treatment onset found that older children made greater gains in weight and height percentiles than younger children, but the difference was not statistically significant.
Correlations between mean dose during treatment vs. change in percentile from onset to final follow-up, and between age at onset of treatment vs. change in percentile from onset to final follow-up, were low in magnitude (0.03 to –0.22 for *r*) and not significant.

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Habel 2011 US (Fair)	Retrospective, population-based cohort study	A: Amphetamines B: Methylphenidate C: Atomoxetine Dosage: NR Duration of exposure was varied (current use, indeterminate use (e.g. <90days after end of current use), former use (90 to 364 days after end of current use), remote use (>365 days since use), non-use)	1986-2002 (follow-up concluded in 2005); 4 study sights (Tennessee state Medicaid data, large insurer [OptumInsight Epidemiology], HMO research network, Kaiser Permanente)	443,198 (unique individuals; 150,359 of which were current users at baseline)
Habel, 2011 US (Fair) Continued.				

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Habel 2011 US (Fair)	Age (median), y: 42 Gender, % female: 54 ADHD medication (current use), no. (%): Amphetamine: 57,824 (37.8) Methylphenidate: 70,923 (46.4) Atomoxetine: 19,283 (12.6)	NR
Habel, 2011 US (Fair) Continued.		

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Habel 2011 US (Fair)	Adjusted Rate Ratios for Serious Cardiovascular Events associated with use vs. non-use of ADHD medications Myocardial Infarction (MI): Amphetamines: RR, 0.92; 95% CI, 0.70 to 1.19 Methylphenidate: RR, 0.89; 95% CI, 0.71 to 1.13 Atomoxetine: RR, 0.87; 95% CI, 0.48 to 1.57 Sudden cardiac death (SCD) Amphetamines: RR, 0.93; 95% CI, 0.52 to 1.63 Methylphenidate: RR, 0.67; 95% CI, 0.38 to 1.18 Atomoxetine: RR, 1.04; 95% CI, 0.38 to 2.82 Stroke Amphetamines: RR, 0.63 95% CI, 0.40 to 1.01 Methylphenidate: RR, 0.94; 95% CI, 0.68 to 1.32 Atomoxetine: RR, 0.44; 95% CI, 0.14 to 1.38 MI, SCD or stroke Amphetamines: RR, 0.85; 95% CI, 0.68 to 1.05 Methylphenidate: RR, 0.87; 95% CI, 0.72 to 1.04 Atomoxetine: RR, 0.74; 95% CI, 0.74 to 1.19	AHRQ, FDA, National Institute of Aging	
Habel, 2011 US (Fair) Continued.	Adjusted Rate Ratios for Serious Cardiovascular Events associated with periods of current use ADHD medications vs. periods remote from last use Myocardial Infarction (MI): Amphetamines: RR, 1.12; 95% CI, 0.83 to 1.52 Methylphenidate: RR, 1.10; 95% CI, 0.83 to 1.45 Atomoxetine: RR, 1.06; 95% CI, 0.57 to 1.96 Sudden cardiac death (SCD) Amphetamines: RR, 0.94; 95% CI, 0.51 to 1.76 Methylphenidate: RR, 0.68; 95% CI, 0.37 to 1.27 Atomoxetine: RR, 1.06; 95% CI, 0.38 to 2.95 Stroke Amphetamines: RR, 0.77 95% CI, 0.46 to 1.29 Methylphenidate: RR, 1.15; 95% CI, 0.77 to 1.72 Atomoxetine: RR, 0.54; 95% CI, 0.17 to 1.71 MI, SCD or stroke Amphetamines: RR, 1.05; 95% CI, 0.82 to 1.34 Methylphenidate: RR, 1.07; 95% CI, 0.86 to 1.34 Atomoxetine: RR, 0.92; 95% CI, 0.56 to 1.50		

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Habel, 2011 US (Fair) Continued.				
Holick 2009 (Fair)	Retrospective cohort	Atomoxetine or stimulant ADHD medication with daily dosage values up to 240 mg Duration: Mean exposure during follow-up not reported, but mean follow-up was 1.5 years	Time Frame: January 1, 2003 through December 31, 2006 Data source: Automated medical and pharmacy claims from the Ingenix Research DataMart	Stimulant ADHD medication=21,606 Atomoxetine=21,606

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Habel, 2011 US (Fair) Continued.		
Holick 2009 (Fair)	After propensity score matching: 52% male 26% age 18-24 years 10% age 25-29 years 24% age 30-39 years 25% age 40-49 years 15% age 50-64 years 1% age ≥ 65 years 45% ADHD 10% hypertension 1% smoking	NR

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Habel, 2011 US (Fair) Continued.	Adjusted Rate Ratios for Serious Cardiovascular Events associated with periods of new use of ADHD medications vs. periods remote from last use Myocardial Infarction (MI): Amphetamines: RR, 0.94; 95% CI, 0.60 to 1.46 Methylphenidate: RR, 1.26; 95% CI, 0.88 to 1.80 Atomoxetine: RR, 1.06; 95% CI, 0.54 to 2.10 Sudden cardiac death (SCD) Amphetamines: RR, 0.38; 95% CI, 0.12 to 1.22 Methylphenidate: RR, 0.69; 95% CI, 0.32 to 1.46 Atomoxetine: RR, 0.90; 95% CI, 0.28 to 2.91 Stroke Amphetamines: RR, 0.77; 95% CI, 0.39 to 1.53 Methylphenidate: RR, 1.44; 95% CI, 0.90 to 2.30 Atomoxetine: RR, 0.64; 95% CI, 0.20 to 2.04 MI, SCD or stroke Amphetamines: RR, 0.87; 95% CI, 0.61 to 1.23 Methylphenidate: RR, 1.20; 95% CI, 0.91 to 1.59 Atomoxetine: RR, 0.91; 95% CI, 0.53 to 1.56		
Holick 2009 (Fair)	Current use, as-treated analyses: atomoxetine versus stimulant ADHD medication; IR=incidence rate per 1000 person-years; RR=crude relative risk (covariate-adjusted models unable to converge due to small number of cases) CVA: IR=0.52 versus 0.38; RR 1.38 (95% CI 0.42 to 4.54) TIA: IR=0.10 versus 0.33; RR 0.31 (95% CI 0.04 to 2.63) As-matched analysis: atomoxetine versus stimulant ADHD medication; HR=hazard ratio adjusted for calendar year CVA: IR=0.32 versus 0.35; HR 0.91 (95% CI 0.39 to 2.16) TIA: IR=0.22 versus 0.29; HR 0.78 (95% CI 0.29 to 2.08)	Contract between i3 Drug Safety, a division of Ingenix Pharmaceutical Services and Eli Lilly and Company	

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Kemner 2006 (Fair)	Retrospective cohort	MPH IR 30 mg vs MPH ER 36 mg Duration: 12 months	Data source: Integrated Health Care Information Services National Managed Care Benchmark Database Data collection period: 2/1/00-12/31/02	5939
Kemner 2006b (OROS MPH vs. TID IR MPH) (Fair)	Retrospective cohort	TID IR MPH: dose not reported OROS MPH: dose not reported 81% of the sample initiated therapy on OROS MPH Duration: 12 months	Data source: Integrated Health Care Information Services National Managed Care Benchmark Database Data collection period: 2/1/00-12/31/02	5939

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Kemner 2006 (Fair)	Mean age=15 years 77% male Race NR	NR
Kemner 2006b (OROS MPH vs. TID IR MPH) (Fair)	Mean age=15 77% male Race NR	OROS MPH vs. TID IR MPH 15 day Gap in ITT medication: 85% vs. 97%, P<0.0001 30 day Gap in ITT medication: 77% vs. 95%, P<0.0001 Switch to another ADHD med: 27% vs. 68%, P<0.0001 Switch to other ITT med: 1% vs. 33%, P<0.0001 Days on ITT medication: 90% compliant: 24% vs. 5%, P<0.0001 80% compliant: 29% vs. 7%, P<0.0001 75% compliant: 30% vs. 5%, P<0.0001 Hospitalizations -- OROS MPH : OR=0.668, P=0.045 (Individuals who received OROS MPH were 33% less likely to be hospitalized compared to individuals who received TID IR MPH)

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Kemner 2006 (Fair)	Table 2. **Factors Affecting Emergency Room Visits and the Number of Visits** Probability of an Emergency Room Visit: Odds Ratio (95% CI)[a], p No. Emergency Room Visits: Point Estimate (95% CI), p Age: 1.00 (0.99 to 1.01), NS; –1.98 (–0.01 to 0.01), NS Female: 1.01 (0.89 to 1.20), NS; 0.00 (–0.13 to 0.17), NS Geographic region East: 1.90 (1.46 to 2.41), <0.0001; 0.00 (0.80 to 1.25), <0.0001 South: 1.40 (0.86 to 2.29), NS; 1.02 (0.43 to 1.29), <0.0001 North Central: 2.50 (1.39 to 4.48), 0.002; 0.86 (0.56 to 1.67), <0.0001 West: 0.99 (0.68 to 1.45), NS; 1.11 (0.69 to 1.31), <0.0001 HMO insurance: 1.04 (0.89 to 1.21), NS; 1.00 (–0.07 to 0.20), NS Total no. diagnoses preinitiation: 1.05 (1.03 to 1.08), <0.0001; 0.05 (0.03 to 0.07), <0.0001 Diagnosis associated with ADHD Anxiety: 1.09 (0.53 to 2.24), NS; –0.12 (–0.78 to 0.54), NS Depression: 0.93 (0.48 to 1.79), NS; –0.25 (–0.84 to 0.35), NS Oppositional disorder: 1.31 (0.095 to 1.81), NS; 0.29 (0.00 to 0.59), 0.05 Drug or alcohol abuse: 2.59 (1.61 to 4.17), <0.0001; 0.88 (0.46 to 1.30), <0.0001 Accident or injury: 37.97 (28.16 to 51.20), <0.0001; 1.95 (1.75 to 2.14), <0.0001 ER methylphenidate: 0.79 (0.60 to 0.95), 0.01; –0.21 (–0.37 to 0.05), 0.01 [a]CI = confidence interval, NS = not significant, HMO = health maintenance organization, ADHD = attention-deficit/hyperactivity disorder.	NR	
Kemner 2006b (OROS MPH vs. TID IR MPH) (Fair)	NR	McNeil Consumer and Specialty Pharmaceuticals	

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Lage 2004 (Fair)	Retrospective cohort	XR MPH TID IR MPH Duration: NR	Data resource: Integrated Health Care information Services (IHCIS) National Managed Care Benchmark Database, December 18, 1999– August 14, 2002.	NR
Marcus 2005 (Fair)	Retrospective cohort	ER-MPH IR-MPH Duration: 12 months	Statewide California Medicaid claims files, January 1, 2000-December 31, 2003	NR
McAfee 2008 US (Fair)	Retrospective cohort	Atomoxetine or other ADHD medications (stimulants and bupropion); dosage not reported Duration: Mean exposure during follow-up not reported	Time Frame: During or before 2003 Data source: Automated medical and pharmacy claims from the Ingenix Research DataMart	Atomoxetine only=982 Other ADHD medications=22,506

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Lage 2004 (Fair)	Mean age=9.73 years 75% male Ethnicity: NR	Treatment pattern- XR MPH vs TID IR MPH, p value Days supplied: 186 vs 127, p<0.0001 Discontinue, stopped receiving all ADHD medications prior to t+1 year-28days: 47% vs 72%, p<0.0001 Switch, stopped prescription for one ADHD medication and started prescription another: 37% vs 59%, p<0.0001 Persist, no discontinuations or gap (>14days): 12% vs 1%, p<0.0001 Covariates of Accident/Injury- Coefficient, Odds ratio(95% CI) XR MPH: -0.5486, 0.578(0.353-0.945) Age(years): 0.1156, 1.123(0.994-1.267) Female: -0.9015, 0.406(0.225-0.734) Preferred provider: -0.5671, 0.567(0.365-0.882) Prior accidents present: 1.0576, 2.879(0.928-8.937) Prior total cost: -0.00024, 1.000(1.000-1.000) Number of chronic medications: -0.1480, 0.862(0.758-0.982) Number of diagnosis: 0.2286, 1.257(1.195-1.321) Intercept: -4.2703
Marcus 2005 (Fair)	Mean age: NR 70% 6-12 years 29% 13-17 years 78% male 45.3% White; 22.9% Black; 26.0% Hispanic; 5.7% Other	Mean treatment duration- ER-MPH vs IR MPH, STR(95% CI) total: 140.3 vs 103.4, 1.37(1.32-1.42) Age 6-12y: 149.5 vs 107.5, 1.38(1.32-1.45) 13-17y: 125.1 vs 91.3, 1.35(1.27-1.43) Gender Male: 140.9 vs 101.8, 1.40(1.34-1.46) Female: 138.4 vs 109.1, 1.27(1.18-1.38) Race White: 154.9 vs 116.8, 1.43(1.35-1.52) Black: 125.7 vs 90.8, 1.37(1.27-1.48) Hispanic: 126.2 vs 94.9, 1.28(1.19-1.38) Other: 130.4 vs 93.9, 1.29(1.10-1.53)
McAfee 2008 US (Fair)	74% male 59% ages 6-12 years 41% ages 13-17 years Seizure risk factors: Congenital=4%, CNS=10%, Systemic=32%, Substance=17%	NR

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Lage 2004 (Fair)	NR	Janssen-Ortho Inc.	
Marcus 2005 (Fair)	NR	McNeil Consumer & Specialty Pharmaceuticals	
McAfee 2008 US (Fair)	Incidence rate of first medical claim of seizure for current use (per 1000 person-years): Atomoxetine=5.9, other ADHD therapy=4.2 Adjusted relative risk (95% CI) of first medical claim of seizure for current use versus nonuse: Atomoxetine=1.1 (0.6 to 2.1); other ADHD therapy=0.8 (0.6 to 1.3); crude and adjusted nested case control analyses did not differ in any meaningful was from the cohort analysis results Seizure risk factors in overall group: Demographics (versus males, age 13-17): Female age 6-12=1.7 (0.9 to 3.3), Female age 13-17=1.4 (0.7 to 3.0), Male age 6-12=1.6 (1.0 to 2.7) Seizure risk factors: Congenital versus no congenital=1.2 (0.5 to 2.4); CNS versus no CNS=4.6 (3.0 to 7.0); systemic versus no systemic=1.1 (0.7 to 1.6); substance versus no substance=1.8 (1.2 to 2.8)	Contract between i3 Drug Safety, a division of Ingenix Pharmaceutical Services and Eli Lilly and Company	

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
McCarthy 2009 UK (Fair)	Retrospective cohort	Methylphenidate Dexamfetamine Atomoxetine Dose, duration of exposure not reported	UK General Practice Research Database, January 1, 1993 to June 30, 2006	N=5351 (18,637 patient-years)
Miller-Horn 2008 U.S. (Fair)	Retrospective cohort (database analysis)	(i) Amphetamine/DEX extended release (Adderall XR) (ii) Amphetamine/DEX (Adderall) (iii) osmotic controlled-released formulation of MPH (OROS) (iv) atomoxetine (Strattera) (v) MPH standard release (MPH) Duration: 24 months	Children treated for ADHD at St. Christopher's Hospital for Children (Philadelphia, PA) neurology clinic over a 24-month period from 2002 to 2004, identified by a retrospective database analysis	137
Olfson 2007 (Fair)	Retrospective, claims data review	ER-MPH IR-MPH Duration: 4 year period of claims data	Pharmacy and medical claims for 75 US managed care plans representing approximately 55 million beneficiaries for dates of service from January 1, 2000 through December 31, 2004	5,122

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
McCarthy 2009 UK (Fair)	Patients aged 2 and 21 years with at least one prescription for methylphenidate, dexamfetamine or atomoxetine.	NR
Miller-Horn 2008 U.S. (Fair)	Mean age males: 9.9 years females: 10.9 years 79.6% male Ethnicity: NR	NR
Olfson 2007 (Fair)	ER-MPH Mean age: 31.2 years 60.3% male Ethnicity NR IR-MPH Mean age: 33.3 years 55.8% male Ethnicity NR	ER-MPH vs IR-MPH Overall median days on treatment: 68.0 vs 39.0 2 or more stimulant pharmacy claims: 61.4% vs 50.5% (p<0.001) Median days on treatment for those with 2 ore more stimulant pharmacy claims: 138 vs 121

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
McCarthy 2009 UK (Fair)	7 deaths total; crude mortality rate 37.6 [per 100,000 patient-years. SMR (calculated indirectly): 1.44 (95% CI 0.58, 2.96) No sudden deaths in 6 patients with a confirmed cause of death. Suicide in 2 patients, overdose of unknown intent in 1 patient. SMR for suicide for children aged 11-14 years 161.91 (95% CI 19.61, 584.88) SMR for suicide for children aged 15-21 years 1.84 (95% CI 0.05, 10.25)	License for the General Practice Research Database funded by the European Commission via the Taskforce European Drug Development for the Young (TEDDY) network of Excellence European Commission Framework 6 Programme 2005-2010. No specific funding was obtained for the conduct of this study.	
Miller-Horn 2008 U.S. (Fair)	35 of 137 reported side effects (25%) Adderall XR vs Adderall vs OROS vs Strattera vs MPH Insomnia: 3.8% vs 22.2% vs 12.5% vs 6.7% vs 8.7% Tics: 0% vs 5.5% vs 2.5% vs 3.3% vs 8.7% Decreased appetite: 15.4% vs 22.2% vs 17.5% vs 10% vs 8.7% Headaches: 11.5% vs 11.3% vs 10% 0% vs 4.3% (P=0.035)	NR	
Olfson 2007 (Fair)	NR	Ortho-McNeil Janssen Scientific Affairs	

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Pilkinton 2012 US	Surveillance observational study	A. Ritalin/methylphenidates B. Adderall Dosage and duration of exposure: NR	Time frame: 2008 Data source: 2009 National Survey of Drug Use and Health	55,635
Pliszka 2006 (Poor)	Retrospective cohort	MPH (any form) vs MAS (any form) Highest daily dosages: 34.8 mg vs 22.7 mg Mean duration: 2.6 years	University-based child and adolescent psychiatry/psychopharmacology clinical database	179
Rabiner 2009 US (Poor)	Survey	ADHD medication. Drug, dose, duration not specified.	Web-based survey conducted in Spring 2007	115

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Pilkinton 2012 US	Overall n, (%): Age: 12-17 y: 17,770 (32) 18-25 y: 19,122 (34) 26-34 y: 5,569 (10) 35-49 y: 7,853 (14) 50 y and older: 5321 (10) % female*: 26,442/50,804 = 52 Ethnicity/Race: White: 34,490 (62) African American: 7212 (13) Hispanic: 9,201 (16) Other: 4831 (9) Educational level: Less than high school: 6,712 (12) High school graduate: 12,705 (23) Some college: 10,904 (20) College degree: 7,544 (14) Between ages 12 and 17: 17,770 (32) *Includes white, African American, and Hispanic respondents.	NR
Pliszka 2006 (Poor)	Mean age=8.7 years 81.0% male Race NR	NR
Rabiner 2009 US (Poor)	College students at two universities with a prescription for ADHD medication; 68.7% female	NR

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Pilkinton 2012 US	% of respondents that used Ritalin nonmedically: 40 % of respondents that used Adderall nonmedically: 1.2 Other harms of interest: NR	Substance Abuse and Mental Health Services Administration Office of Applied Studies	
Pliszka 2006 (Poor)	Final Z scores for MAS vs MPH: Height: 0.0 vs -0.2 Weight: 0.4 vs 0.6 BMI: 20.1 vs 20.9 No main effects for either stimulant type on height, weight or BMI	NR	
Rabiner 2009 US (Poor)	31% reported having taken their medicine more often than prescribed, at a higher dose than prescribed, or using someone else's medication since beginning college. 8% reported snorting their medication during the past 6 months 1 student reported injecting medication in the past 6 months 56% were approached by a peer to give or sell them their medication in the past 6 months. 25% reported giving or selling their medication to a peer in the past 6 months. Students who had misused their ADHD medication were more likely to divert their medication than those who had not (59% vs 22%; P<0.001).	NIDA Grant R21-DA018754	

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Safer 1972 US (Fair)	Retrospective analysis of height and weight data Comparative	Group 1: MPH 28.7 mg/day DEX 11.8 mg/day Group 2: MPH continuous treatment for 2+ years (dose not reported; 7 of 9 subjects were also in group 1 above) Control group: no medication Duration: Group 1: 1 year Group 2: 2+ years	Patients in one of the following 2 groups: 1) hyperactive children who had been on stimulant medication for 9 months and had been either kept on or taken off treatment during the 3-month summer period; 2) hyperactive children, some who received continuous medication for 2+ years, and some who received no medication.	29
Safer 1973 US (Fair)	Retrospective cohort (student health records)	DEX MPH Unmedicated controls Mean dosages NR Duration: ≥ 2 years	Forms completed by school nurses in six elementary schools in Baltimore, Maryland for all hyperactive children in their school who received stimulant medication for two or more years. Time frame NR.	44 on medication, 14 unmedicated controls

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Safer 1972 US (Fair)	Group 1: Mean age 9.8 Gender NR 100% white Group 2: Mean age NR Gender NR Ethnicity NR	NR
Safer 1973 US (Fair)	Mean age NR 89.8% male in children on medication; 100% male in unmedicated control group 100% white	NR

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

<table>
<tr><th>Author, year
Country</th><th>Harms</th><th>Funder</th><th>Comments</th></tr>
<tr><td>Safer 1972
US
(Fair)</td><td>
<table>
<tr><th rowspan="2">Group 1</th><th rowspan="2">N</th><th rowspan="2">Dose of MPH mg/day</th><th rowspan="2">Dose of DAMP mg/day</th><th colspan="2">Weight gain in school year (Sept-June), kg/mo</th><th colspan="3">Weight gain in summer (June-July-Aug), kg/mo</th></tr>
<tr><th>All patients</th><th>All on MPH vs all on DAMP</th><th>All patients</th><th>Patients on MPH</th><th>Patients on DAMP</th></tr>
<tr><td>Continued meds. in summer</td><td>7</td><td>37.5</td><td>11.7</td><td>0.15</td><td rowspan="3">0.23 vs 0.12 (p<0.05)</td><td>0.22 (60% of expected gain)</td><td>0.29</td><td>0.14</td></tr>
<tr><td>Discontinued meds. in summer</td><td>13</td><td>24.0</td><td>11.8</td><td>0.17</td><td>0.45 (130% of expected gain)</td><td>0.41</td><td>0.47</td></tr>
<tr><td>P-value, Continued vs Discontinued</td><td></td><td>p<0.05</td><td>ns</td><td>ns</td><td>p<0.05</td><td>ns</td><td>p<0.01</td></tr>
<tr><td colspan="8">DAMP's effects on weight gain did not differ between doses of 10 and 15 mg/day.
MPH 20 mg/day showed significantly greater weight gains than 30 and 40 mg/day.</td></tr>
<tr><th rowspan="2">Group 2</th><th rowspan="2">N</th><th colspan="2">Average percentile changes in growth over 2 or more years</th><td colspan="6" rowspan="2">Mean yearly weight gain of children on stimulants for 2 years was 1.8kg, compared with expected gain of 3.1 kg. Mean percentile for weight decreased from 62nd to 40th.</td></tr>
<tr><th>Weight</th><th>Height</th></tr>
<tr><td>Medication 2+ years</td><td>9</td><td>-17.5</td><td>-16.3</td></tr>
<tr><td>No medication</td><td>7</td><td>+1.3</td><td>+4.0</td></tr>
<tr><td>P-value, Medicated vs. Not</td><td></td><td colspan="2">p<0.05 p<0.05</td></tr>
</table>
</td><td></td><td>The school nurse determined the use of medication during summer based on the children's self-report. At the start of the following school year, the nurse would ascertain if their parents had kept them on medication during the summer.</td></tr>
<tr><td>Safer 1973
US
(Fair)</td><td>DEX; MPH: high-dose (> 20 mg), all, low-dose (≤ 20 mg); controls
Percentile changes in:
Weight: -20.38; -10.0, -6.35, -2.7, +6.79
DEX > all MPH dosage groups and controls; MPH high-dose and all doses > controls; MPH low-dose=controls

Height: -13.45; -9.40, -5.20, -1.00; +1.29
DEX > MPH all-dosage, low-dosage and control groups, but DEX=MPH high-dosage group; MPH high-dosage > controls; MPH all-dosage and low-dosage=controls

All differences remained significant following a covariance analysis that controlled for differences in initial values of weight and height percentiles</td><td>NR</td><td>Initial weight/height percentile values were initially larger for DEX group</td></tr>
</table>

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Safer 1975 (Poor)	Prospective cohort study	MPH: 27 mg/day, range 10-60mg DEX 12 mg/day, range 5-20mg Duration: 1 year	Hyperactive students at one elementary school in a suburban, blue-collar, Caucasian area from 1970-1973	NR
Sanchez 2005 (Fair)	Retrospective cohort	MPH IR, MPH SR, MPH ER, MPH OROS, MAS IR, DEX IR, DEX ER Duration: 6 months	Texas Medicaid recipients aged 5-18 years with continuous paid prescription claims from June 1, 2001-May 31, 2002	9,549
Schelleman 2011 US (Fair)	Retrospective cohort	Amphetamines Atomoxetine Methylphenidate Dose and duration of use not reported; analyzed those with fewer than 180 days of use and those with at least 180 days	Data from 2 US populations (i.e. a 5-state Medicaid database [1999-2003] and the 14-state HealthCore Integrated Research Database [2001-2006]) Linked Medicare data on Medicaid-Medicare dual eligible patients.	93,470 incident users of amphetamines 19,830 of atomoxetine 128,668 matched nonusers

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Safer 1975 (Poor)	Mean age: 10.3 years, range 8-13 years Gender: 80% male 100% Caucasian	NR
Sanchez 2005 (Fair)	Mean age=9.93 years 75.7% male Ethnicity NR	<u>Comparisons among stimulant groups (MAS IR vs MPH IR vs MPH OROS)</u> Persistence: 0.42 vs 0.37 vs 0.50 (F=159, df=2, p<0.0001) MPR: 0.73 vs 0.69 vs 0.76 (F=32, df=2, p<0.001) 150-180 day treatment duration (% pts): 19% vs 14% vs 30% (c^2=327, df=10, p<0.00) <u>Comparisons among age groups for all drugs combined (5-9 yrs vs 10-14 yrs vs 15-18 yrs)</u> Persistence: 0.45 vs 0.41 vs 0.41 (F=21.6, df=2, p<0.001) MPR: 0.73 vs 0.73 vs 0.67 (F=11.8, df=2, p<0.001)
Schelleman 2011 US (Fair)	Subjects aged 3 to 17 years who were dispensed a solid oral dosage of amphetamines, atomoxetine, or methylphenidate.	NR

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Safer 1975 (Poor)	Compare growth rate in school year and summer Continued group (CG): growth rate of the height and weight, NS Discontinued group (DG): DEX, weight- school year<summer, p<0.005 DEX, height- school year< summer, p<0.05 MPH, weight- school year<summer, p<0.005 MPH, height- school year< summer, p<0.05	NR	
Sanchez 2005 (Fair)	NR	Unclear	
Schelleman 2011 US (Fair)	Incident users vs nonusers (Adjusted hazard ratios, 95% CI) Sudden death or ventricular arrhythmia: Methylphenidate: 2.63 (0.29, 23.69) Any ADHD medication: 1.60 (0.19, 13.60) All-cause death: Amphetamines: 0.95 (0.52, 1.71) Methylphenidate: 0.61 (0.30, 1.25) Any ADHD medication: 0.76 (0.52, 1.12) Nonaccidental death: Amphetamines: 0.41 (0.14, 1.19) Methylphenidate: 0.85 (0.31, 2.32) Any ADHD medication: 0.53 (0.29, 0.99) Nonsuicide death: Amphetamines: 0.60 (0.28, 1.29) Methylphenidate: 0.68 (0.30, 1.54) Any ADHD medication: 0.65 (0.40, 1.04) Other outcomes/drugs not estimable due to low numbers of events	Shire	

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Schelleman 2011 US (Fair) Continued.				
Setlik 2009 US (Poor)	Retrospective cohort	Amphetamine/DEX, MPH (including D-MPH) Duration: NR	Time frame: 1998-2005 Data source: American association of poison control center's national poison data system	Unclear
Thompson 2006 (Poor)	Retrospective study	IR psychostimulant SR MPH Duration: Unclear. Study population consisted of patients taking IR psychostimulant any time between Feb 2002-Feb 2004 2 year period	Patients identified from computer database and personal case load records, February 2002-February 2004	103

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Schelleman 2011 US (Fair) Continued.		
Setlik 2009 US (Poor)	NR	NR
Thompson 2006 (Poor)	12 years 9 months (range 6-17 years) 83.5% male NR	Good response on IR psychostimulant: 88.6% Good response on switching to SR MPH: 64.9%, difference between both response significant p<0.001 % of people switching back to IR psychostimulant from SR MPH=27%, p<0.0001

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Schelleman 2011 US (Fair) Continued.	Prevalent users vs nonusers (Adjusted hazard ratios, 95% CI) Sudden death or ventricular arrhythmia: Methylphenidate: 1.30 (0.15, 11.14) Any ADHD medication: 1.43 (0.31, 6.61) Stroke: Any ADHD medication: 0.89 (0.11, 7.11) All-cause death: Amphetamines: 0.92 (0.48, 1.76) Methylphenidate: 0.79 (0.48, 1.29) Any ADHD medication: 0.77 (0.56, 1.07) Nonaccidental death: Amphetamines: 0.27 (0.06, 1.18) Methylphenidate: 0.64(0.29, 1.40) Any ADHD medication: 0.43 (0.24, 0.79) Nonsuicide death: Amphetamines: 0.97 (0.45, 2.11) Methylphenidate: 0.65 (0.35, 1.20) Any ADHD medication: 0.66 (0.44, 1.00) Other outcomes/drugs not estimable due to low numbers of events		
Setlik 2009 US (Poor)	Amphetamine/DEX related calls increased to 476%, p=0.003 per year Prescriptions for amphetamine/DEX increased 133% (p=0.0004) for 3-19 yr olds and 141% (p≤0.0001 for 10-19 yr olds No. of teen amphetamine/DEX abuse calls per million prescriptions increased 140%(p=0.0005) Methamphetamine related calls decreased by 30% (p=0.003). Prescription for MPH increased 52%(p=0.0038) for 3-19 yr olds and 57% for 10-19 yr olds(p=0.0019) No. of teens MPH abuse calls per million prescription of MPH for 10-19 yr old decreased 55% (p=0.0001) % of patients with moderate, major effects, death in amphetamine/DEX vs MPH groups: 45% vs 37%p<0.001.	Funding for acquisition of IMS health national disease and therapeutics index prescription data supplied by RADARS system, a governmental non-profit operation of the Rocky Mountain Poison and Drug Center, Agency of Denver Health and Hospital Authority	
Thompson 2006 (Poor)	NR	NR (reported that there were no declarations of interest)	

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Winterstein 2009 US (Fair)	Retrospective cohort	MPH or MAS. Dosage NR. Follow-up time, months , mean (SD) amphetamine vs MPH users: 19.2 (18.8) vs 22.5 (23.8)	Time frame: July 1994 to June 2004 Data source: Florida Medicaid fee-for-service program	Amphetamine users: 12338 MPH users: 18238

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Winterstein 2009 US (Fair)	Age at first assignment to group: Range 8.3 to 9.2 years Male: 72% Ethnicity White:44 to 51% Black: 27.9 to 34.7% Hispanic: 14.4 to 16% Concomitant use of antidepressants: 14 to 21% Concomitant use of antipsychotics: 8 to 12.7% Congenital anomalies: 1.6% History of circulatory disease/symptoms: 1.9% Previous hospital admission for any cause: 2.9%	NR

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Evidence Table 3. Data abstraction of observational studies in children and adults with attention deficit hyperactivity disorder

Author, year Country	Harms	Funder	Comments
Winterstein 2009 US (Fair)	Emergency department visits for cardiac causes after adjusting for covariates Current use Adjusted HR 1.01(0.80 to 1.28), unadjusted RR 0.95 (95% CI0.74 to 1.21) Former use Adjusted HR 0.95 (95% CI 0.73 to 1.25), unadjusted RR 1.05 (0.78 to 1.42) Variables showing positive association with emergency department visits among current and former users Current use comparison use of bronchodilators: HR 1.88 (95% CI 1.40 to 2.53) use of antidepressants: HR 1.67 (95% CI 1.29 to 2.15) use of antipsychotics: HR 1.90 (95% CI 1.26 to 2.16) congenital anomalies: HR 3.12 (95% CI 2.22 to 4.38) history of circulatory disease or cardiac symptoms: HR 2.72 (95% CI 1.85 to 4.01) Switching patterns indicating intolerability % of patients on MPH switching to amphetamine 26.8% % of amphetamine users switching to MPH: 23.9%	Florida department of Health, Agency for Healthcare Administration Partly by grant received by Dr. Gerhard from Agency for healthcare Research and Quality U18HSO16097	

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Evidence Table 4. Quality assessment of observational studies in children and adults with attention deficit hyperactivity disorder

Author, Year	Non-biased selection?	Loss to follow-up specified? If yes, low overall loss to follow-up? *(prior to Update 5)*	High overall loss to follow-up or differential loss to follow up? *(Update 5)*	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Barbaresi 2007	Yes	Yes 16.8% moved; 1.9% had unknown graduation drop out status	*Not rated*	Yes	Yes
Charach 2006	No; only 87% of children who completed 12-month RCT were enrolled	No; Overall withdrawal rate of 25% at year 5	*Not rated*	Yes	Yes
Charles 1981	No; excluded 36 (36.7%)	N/A	*Not rated*	No	No
Garnier 2010	Unclear; screened all students at new student orientation; not clear if total sample was all new students or a selection of them	*Not rated*	High loss: 483/1253 who entered were analyzed (38.5%)	Yes	Yes
Germinario 2013	Yes	N/A	*Overall=yes (42% to 47%at 12 months and 184% to 86%at 24 months)* *Differential: No*	Yes	Yes
Goldman 2008	Unclear; all subjects w/ RS eligible	No	*Not rated*	Only RS	Yes
Gross 1976	No	No	*Not rated*	Yes	Yes
Habel 2011	Yes	N/A	*Unclear; no info on handling of missing data*	Yes	Yes
Holick 2009	Yes	*Not rated*	No	Yes	Yes

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Evidence Table 4. Quality assessment of observational studies in children and adults with attention deficit hyperactivity disorder

Author, Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating	Comments
Barbaresi 2007	Yes	No; controlled for age and grade	Yes	Fair	
Charach 2006	Unclear who collected measurements and whether they were blinded to medication status	Yes	Yes	Poor	
Charles 1981	No	No	Yes	Fair/Poor	
Garnier 2010	Potential for bias: trained interviewers, but face-to-face interviews and sensitive information, no verification	Yes	Yes	Poor	
Germinario 2013	Yes	No	Yes	Poor	
Goldman 2008	Yes	Unclear; used case control sample based on demographics.	N/A; retrospective study of patients within a 5 year period	Fair/Poor	Retrospective case control study looked at RS only. Limited description of case control sample.
Gross 1976	Yes	NR	Yes	Fair	Study included only patients within the investigator's clinical practice, for whom pre-treatment weight and height data were available
Habel 2011	Yes	Yes	Yes	Fair	
Holick 2009	Unclear; medical record review was only possible for 77% of CVA's and 78% of TIA's, and resulting confirmations were less than 33%	Yes	Yes; mean=1.5 years	Fair	

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Evidence Table 4. Quality assessment of observational studies in children and adults with attention deficit hyperactivity disorder

Author, Year	Non-biased selection?	Loss to follow-up specified? If yes, low overall loss to follow-up? *(prior to Update 5)*	High overall loss to follow-up or differential loss to follow up? *(Update 5)*	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Kemner 2006/Lage 2004	Yes	No	*Not rated*	Yes	Yes
Kemner 2006b (OROS MPH vs. TID IR MPH)	Yes	No	*Not rated*	Yes	Yes
Lage 2004	Yes	N/A	*Not rated*	Yes	Yes
Marcus 2005	Unclear	N/A	*Not rated*	Yes	Yes
McAfee 2008	Unclear; database inclusion criteria does not specify new users	*Not rated*	Unclear; patients with less than one year of coverage excluded from analysis	Yes	Yes
McCarthy 2009	Yes; database; inclusion criteria specified	*Not rated*	No - response 100%	Yes	Yes
Miller-Horn 2008	No; first 150 entered into the database were included	N/A	*Not rated*	Yes	Yes
Olfson 2007	Yes	No loss to follow-up	*Not rated*	Yes	Yes

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Evidence Table 4. Quality assessment of observational studies in children and adults with attention deficit hyperactivity disorder

Author, Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating	Comments
Kemner 2006/Lage 2004	Yes	Yes; controlled for demographic characteristics, general health status, comorbid diagnoses associated with diagnosis of ADHD and use of ADHD medications	Yes	Fair	
Kemner 2006b (OROS MPH vs. TID IR MPH)	Yes	Yes; controlled for demographics, health status, comorbid diagnosis, and use of ADHD medications	Yes	Fair	
Lage 2004	Yes	Yes	Yes	Fair	
Marcus 2005	Yes	Yes	Yes	Fair	
McAfee 2008	Yes; reviewer blinded to ADHD diagnosis determined seizure diagnosis	Yes	Yes	Fair	
McCarthy 2009	Yes	No; descriptive statistics only for mortality; compared suicide rate in cohort to suicide rate in general population adjusted for age and sex only	Yes	Fair	
Miller-Horn 2008	Yes	NR	N/A; retrospective study of patients over a 24 month period	Fair	Open-label retrospective study
Olfson 2007	Yes	Yes; statistical analysis was done controlling for age, gender, treating specialist, other treated mental disorders, claims for other prescribed psychotropic medications, claims for ER and inpatient services in which the first listed diagnosis is mental disorder	Yes	Fair	

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Evidence Table 4. Quality assessment of observational studies in children and adults with attention deficit hyperactivity disorder

Author, Year	Non-biased selection?	Loss to follow-up specified? If yes, low overall loss to follow-up? *(prior to Update 5)*	High overall loss to follow-up or differential loss to follow up? *(Update 5)*	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Pliszka 2006	Yes	Yes; No - 3-year analysis excluded 65% of patients	*Not rated*	Yes	Yes
Rabiner 2009	Unclear; all sophomores and random sample of other classes at 2 universities invited to participate, but total sample not clear	*Not rated*	Possible bias: 28% of surveys at public university and 45% at private university were completed	Yes	Yes; self-administered web-based survey
Safer 1972	No	Yes	*Not rated*	Yes	No
Safer 1973	Yes	No	*Not rated*	No	Yes
Safer 1975	Yes	No	*Not rated*	Yes	No
Sanchez 2005	Yes	N/A	*Not rated*	Yes	Yes
Schelleman 2011	Yes; all subjects meeting inclusion criteria were selected (time-frame not specified)	*Not rated*	No	Yes	Yes
Setlik 2009	No; calls to poison control centers used as proxy for estimating level of abuse (although unbiased sampling of calls- used all calls over an 8-year period)	*Not rated*	Final outcome determined in 64% of calls; no info on other missing data	Yes	Yes

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Evidence Table 4. Quality assessment of observational studies in children and adults with attention deficit hyperactivity disorder

Author, Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating	Comments
Pliszka 2006	Yes	Adjusted for age and time	Yes	Poor	
Rabiner 2009	Outcomes not verified	No; descriptive statistics only	Yes	Poor	
Safer 1972	No	NR	Yes	Fair	Main outcome (percentile change) uses two time points (single baseline measurement taken at school admission at age 5-6, to end of 2+ year treatment) rather than construction of individual growth curves. Classification of treatment during summer based on child's self-report, rather than prescription records.
Safer 1973	No	Yes	Yes	Fair	
Safer 1975	Unclear	No	Yes	Poor	
Sanchez 2005	Yes	No	Yes	Fair	
Schelleman 2011	Yes	Yes; but because of low event rates, adjusted for confounders using exclusion	Yes	Fair	
Setlik 2009	Potential for bias: data collected by phone and not verified	No	Yes	Poor; no control for confounders in analysis of trends - data extrapolated from a sample of physicians to all prescriptions in the US	

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Evidence Table 4. Quality assessment of observational studies in children and adults with attention deficit hyperactivity disorder

Author, Year	Non-biased selection?	Loss to follow-up specified? If yes, low overall loss to follow-up? *(prior to Update 5)*	High overall loss to follow-up or differential loss to follow up? *(Update 5)*	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Thompson 2006	Unclear; no data on recruitment	Yes; 5% data unavailable	*Not rated*	Unclear; had standardized form	No
Winterstein 2009	Yes; database; inclusion criteria specified; 180 days without a prescription	*Not rated*	No	Yes	No

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Evidence Table 4. Quality assessment of observational studies in children and adults with attention deficit hyperactivity disorder

Author, Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating	Comments
Thompson 2006	Unclear; no information on the form or data collection techniques	NA (single-group study)	Unclear	Poor	
Winterstein 2009	No verification of outcomes reported	Yes	Yes	Fair	

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Evidence Table 5. Data abstraction of abuse and diversion studies in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Fredericks 2005 (Poor)	Children 10-14 years with established ADHD taking methylphenidate	Maintenance doses were encapsulated for each participant (three participants with 10 mg, one with 20 mg and one with 30 mg) Total 3 weeks Participants were given MPH or placebo and were to take that except for the six sampling sessions where participants had a chance to experience both drugs and six choice sessions where participants had the opportunity to choose their preference (Methylphenidate or placebo or neither)	NR	Mean age=12 yrs Gender: 80% male Ethnicity: NR	All participants had current prescription for MPH for treatment of ADHD symptoms and have been taking immediate-release MPH treatment for at least 1 yr prior to the study
Oesterheld 1998 (Poor)	Native American child 5 to 12 years with full or partial fetal alcohol syndrome with ADHD	Methylphenidate 0.6 mg /kg 5 days-lactose placebo 5 days and vitamin C placebo 2 days off in between Total 3 weeks	None	Mean age=8.25 yrs Gender: 50% male Ethnicity: 100% Native American	2 boys full FAS 2 girls partial FAS

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Evidence Table 5. Data abstraction of abuse and diversion studies in children and adults with attention deficit hyperactivity disorder

Author, Year Country Trial name (Quality rating)	N	Number withdrawn/ lost to follow-up/ analyzed	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Fredericks 2005 (Poor)	5	0/ 0/ 5	Differences between the number of MPH, Placebo, and Neither choices across participants were significant ($X^2 = 9.6$; $p < 0.01$). Three of five participants reliably chose MPH more often than placebo. MPH produced idiosyncratic patterns of participant-rated effects but failed to produce significant clinical effects.	NR	NR	NR	
Oesterheld 1998 (Poor)	4	NA	CPRS-48 Hyperactivity-Impulsivity scale: F=4.34, df 4, P< 0.05; the daydreaming attention scale was NS CTRS-39 Hyperactivity-Impulsivity scale: F=6.42, df 4, P<0.02	During active treatment: Decreased appetite: 75% Stomach ache: 50% Headache: 50%	Total: 0 Due to AEs: 0	U of South Dakota: USF-Minigrant 94 202-4590-005	

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Evidence Table 6. Quality assessment of abuse and diversion studies in children and adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intent-to-treat analysis
Fredericks 2005	Yes; the order in which placebo and MPH were scheduled in the sampling sessions was counter-balanced across subjects and within-subjects across weeks	Yes	Yes; only 5 participants	Yes	Yes	Yes; medication dispensers blinded	Yes	NR
Oesterheld 1998	NR	Unclear	Yes; only 4 participants	Yes	Yes	Yes	Yes	NR

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Evidence Table 6. Quality assessment of abuse and diversion studies in children and adults with attention deficit hyperactivity disorder

Author, Year	Post-randomization exclusions *(prior to Update 5)*	Maintenance of comparable groups *(Update 5)*	Loss to follow-up: differential/high *(prior to Update 5)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 5)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 5)*	Quality Rating
Fredericks 2005	No	*Not rated*	No/No	NA	*Not rated*	Poor; not sure how to rate this study
Oesterheld 1998	No	*Not rated*	No/No	NA	*Not rated*	Poor; not sure how to rate this study

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