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A Comparison of the Efficacy of Medications for Adult Attention-Deficit/Hyperactivity Disorder Using Meta-Analysis of Effect Sizes

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Article Abstract

Objectives: Medications used to treat attention-deficit/hyperactivity disorder (ADHD) in adults have been well researched, but comparisons among drugs are hindered by the absence of direct comparative trials. Our objectives were to (1) estimate the effect size of the medications used to treat adult ADHD, (2) determine if differences in the designs of studies confound comparisons of medication efficacy, (3) quantify the evidence for differences in effect sizes among medications, and (4) see if features of study design influence estimates of efficacy.

Data Sources: The following search engines were used: PubMed, Ovid, ERIC, CINAHL



and Adolescent Psychiatry meetings were reviewed.

Study Selection: A literature search was conducted to identify double-blind, placebo-controlled studies of ADHD in adults published in English after 1979. Only trials that used DSM-III, -III-R, or -IV ADHD criteria and followed subjects for ≥ 2 weeks were selected.

Data Extraction: Meta-analysis regression assessed the influence of medication type and study design features on medication effects.

Results: Nineteen trials met criteria and were included in this meta-analysis. These trials studied 13 drugs using 18 different outcome measures of hyperactive, inattentive, or impulsive behavior. After trials were stratified on the class of drug studied (short-acting stimulant vs long-acting stimulant vs nonstimulant), significant differences in effect size were observed between stimulant and nonstimulant medications ($P = .006$ and $P = .0001$, respectively, for short- and long-acting stimulants vs nonstimulants), but the effect for short-acting stimulants was not significant after correcting for study design features. The effect sizes for each drug class were similar in magnitude to what we previously reported for medication treatment studies of children with ADHD. We found significant heterogeneity of effect sizes for short-acting stimulants ($P < .001$) but not for other medication groups.

Conclusions: Although both stimulant and nonstimulant medications are effective for treating ADHD in adults, stimulant medications show greater efficacy for the short durations of treatment characteristic of placebo-controlled studies. We found no significant differences between short- and long-acting stimulant medications. Study design

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Conclusions: Although both stimulant and nonstimulant medications are effective for treating ADHD in adults, stimulant medications show greater efficacy for the short durations of treatment characteristic of placebo-controlled studies. We found no significant differences between short- and long-acting stimulant medications. Study design features vary widely among studies and can confound indirect comparisons unless addressed statistically as we have done in this study.

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Attention-deficit/hyperactivity disorder (ADHD) is a neurocognitive disorder with a high worldwide prevalence.¹ For decades, the stimulant medications methylphenidate, dextroamphetamine, and mixed amphetamine salts have been the most common drugs used in the treatment of ADHD. Stimulant medications reduce the overactivity, impulsivity, and inattention characteristic of patients with ADHD and improve associated behaviors, including on-task behavior, academic performance, and social functioning.²

Although stimulants have been the mainstay of ADHD pharmacotherapy for many decades, several nonstimulant medications have also shown evidence of efficacy. One of these, atomoxetine, is approved by the US Food and Drug Administration for the treatment of ADHD in adults. The others include tricyclic antidepressants,³⁻⁵ bupropion,⁶⁻⁸ modafinil,^{9,10} monoamine oxidase inhibitors,^{11,12} guanfacine,¹³ and clonidine.¹⁴

While the medications that treat ADHD have been well researched, comparisons among drugs are hindered by the absence of head-to-head trials. In the absence of such trials, physicians must rely on qualitative comparisons among published trials, along with their own clinical experience, to draw conclusions about the efficacy of different medication types on ADHD outcomes. Qualitative reviews of the literature are useful for summarizing results and drawing conclusions about general trends, but they cannot easily evaluate and control the many factors associated with study design that influence the apparent medication effect from a single study.

use different outcome measures. Comparing such studies is difficult because the meaning of a 1-point difference between drug and placebo groups on a particular outcome measure is typically not the same as the meaning of a 1-point difference on another outcome measure. Meta-analysis partially solves this problem by computing an effect size for each measure. The effect size standardizes the unit of measurement across studies so that a change in 1 point on the effect size scale has the same meaning in each study. For example, in the case of the effect size known as the standardized mean difference (SMD), a 1-point difference means that the drug and placebo groups differ by 1 standard deviation on the outcome measure.

Comparing effect sizes between studies is questionable if the studies differ substantially on design features that might plausibly influence drug-placebo differences. For example, if one study used a crossover design and the other a parallel design, we could not be sure whether the difference in effect size were due to differences in drug efficacy or differences in methodology. Or, if a study of one drug used physician ratings and the other used self ratings, the difference between studies could be due to the different raters used, not the different drugs. Meta-analysis can address this issue by using regression methods to determine if design features are associated with effect size and if differences in design features can account for differences among drugs.

The present study applies meta-analysis to published literature on the pharmacotherapy of ADHD in adults. For youth with ADHD, there have been prior meta-analyses of medication treatment¹⁵⁻¹⁷ and reviews of effect size for long-acting formulations.¹⁸ There are 2 meta-analyses of treatment for adult ADHD. One is limited to methylphenidate.¹⁹ The

work sought to (1) estimate the effect size of the different medications used to treat adult ADHD, (2) determine if differences in the designs of studies might have confounded comparisons of medication efficacy, (3) quantify the evidence for significant differences in effect sizes among medications, and (4) see if features of study design influence the estimate of medication efficacy.

METHOD

A literature search was conducted to identify double-blind, placebo-controlled studies of ADHD in adults published in English after 1979. We searched for articles using the following search engines: PubMed, Ovid, ERIC, CINAHL, MEDLINE, PREMEDLINE, the Cochrane database, e-psyche, and Social Sciences Abstracts. In addition, presentations from the American Psychiatric Association and American Academy of Child and Adolescent Psychiatry meetings were reviewed. We included only studies using randomized, double-blind methodology with placebo controls that defined ADHD using diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (*DSM-III*); Third Edition, Revised (*DSM-III-R*); or Fourth Edition (*DSM-IV*), and that followed subjects for 2 weeks or more. To be included, studies must have presented the means and standard deviations of either change or endpoint scores for the drug and placebo groups. Some studies titrated patients to an optimal dose, whereas others titrated subjects to one of several fixed doses. Because it would not be fair to compare low fixed-dose treatment with optimally titrated treatment, for studies presenting data on more than 1 fixed dose, we used the highest dose. We excluded studies that rated behavior in laboratory environments, studied fewer than 20 subjects in either the drug or placebo groups, were designed to explore appropriate doses for future

we extracted the following data from each article: name of dependent outcome measure, name of drug, distribution of *DSM-IV* subtypes in study sample (for studies using *DSM-IV* criteria), design of study (parallel vs crossover), type of outcome score used (change score vs posttreatment score), type of rater (clinician, self), mean age of study sample, percentage of male subjects in study sample, dosing method (fixed dose vs titration to best dose), exclusion of nonresponders (yes/no), use of placebo lead-in (yes/no), and year of publication.

We analyzed 3 types of scores: total ADHD scores (either symptom counts or global ADHD symptom improvement ratings), hyperactive-impulsive symptom scores, and inattentive symptom scores. Effect sizes for dependent measures in each study were expressed as SMDs. The SMD is computed by taking the mean of the active drug group minus the mean of the placebo group and dividing the result by the pooled standard deviation of the groups. Studies reporting change scores provided endpoint minus baseline scores for drug and placebo groups. In this case, the SMD is computed as the difference between change scores. For studies reporting endpoint scores, the SMD is computed as the difference between endpoint scores. Our meta-analysis used the random-effects model of DerSimonian and Laird,²¹ which weights the effect of each study by its sample size. We used meta-analytic regression to assess the degree to which the effect sizes varied with the methodological features of each study described above. We estimated a separate model for each feature. The meta-analyses and meta-analytic regressions were weighted by the reciprocal of the variance of the effect size. We used Egger's²² method to assess for publication biases. We also assessed the number needed to treat (NNT), which is the number of patients who need to be treated to prevent 1 bad outcome. The NNT is typically computed as the inverse of the difference between the response rate on treatment and the

continuous variables if we assume that a treated patient has a successful outcome if the patient's outcome is better than it would have been had they been given placebo rather than medication. They then compute $NNT = 1 / [(2 \times \text{normal}[SMD / \sqrt{2}]) - 1]$ where "normal(Z)" is the probability that a randomly selected standard normal variable is less than Z.

For each study, all dependent outcome measures reported were treated as a separate data point for entry into the analysis, with several studies providing data on more than 1 measure to permit comparison of measures as well as among drugs in this population. Because measures reported from the same study are not statistically independent of one another, standard statistical procedures will produce inaccurate *P* values. To address this intrastudy clustering, variance estimates were adjusted using Huber's²⁴ formula as implemented in STATA.²⁵ This formula is a "theoretical bootstrap" that produces robust statistical tests. The method works by entering the cluster scores (ie, sum of scores within families) into the formula for the estimate of variance. The Huber estimate is also called the "sandwich" estimate because it is calculated as the product of 3 matrices: the matrix formed by taking the outer product of the observation-level likelihood score vectors is in the middle, and this matrix is premultiplied and postmultiplied by the usual model-based variance matrix. The resulting *P* values are valid even when observations are not statistically independent. This approach was applied consistently for all studies.

RESULTS

[Table 1](#) describes the 18 articles meeting criteria for inclusion in the meta-analysis. Studies are listed more than once if they studied more

provided information on more than one outcome score. These allowed us to compute 60 effect sizes. [Table 2](#) shows the number of times each medication was studied and the numbers of subjects in the drug and placebo groups from those studies.

 [Table 1](#)

Click figure to enlarge

 [Table 2](#)

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[Figure 1](#) shows the results for long-acting stimulants. The mean effect size of 0.73 for long-acting stimulants is statistically significant ($z = 13.0$, $P < .001$). There was no significant heterogeneity among effect sizes ($\chi^2_{10} = 6.2$, $P = .8$). [Figure 2](#) shows the results for short-acting stimulants. The mean effect size of 0.96 is statistically significant ($z = 7.0$, $P < .001$), but there was significant heterogeneity among effect sizes ($\chi^2_{17} = 58$, $P < .001$). [Figure 3](#) shows results for nonstimulants. The mean effect size of 0.39 is statistically significant ($z = 13.9$, $P < .001$). There was no significant heterogeneity among effect sizes ($\chi^2_{30} = 25$, $P = .8$).

Because [Figure 3](#) suggests that our failure to find heterogeneity for nonstimulants was accounted for by the atomoxetine studies, we reran the heterogeneity analyses separately for atomoxetine and other nonstimulants. There was no significant heterogeneity among effect sizes for atomoxetine ($\chi^2_{16} = 6.1$, $P = 1.0$) or for the other nonstimulants ($\chi^2_{13} = 16.2$, $P = .24$).

 [Figure 1](#)

 [Figure 3](#)

Click figure to enlarge

We conducted separate random-effects meta-analyses for each class of medication to assess for publication bias. We found no evidence of publication bias for the nonstimulants ($t_{30} = 1.7, P = .09$) or the long-acting stimulants ($t_{10} = 0.8, P = .5$). There was evidence of publication bias for short-acting stimulants ($t_{17} = 4.7, P < .001$). The trim and fill method to correct for publication bias⁴³ suggests that the pooled estimate of effect size for the short-acting stimulants (0.96) is an overestimate of a true effect size of 0.86.

Meta-analysis regression found a significant effect of drug type ($F_{2,18} = 10.9, P = .0008$). The effect sizes for nonstimulant medications were significantly less than those for short-acting stimulants ($t_{18} = 3.1, P = .006$) and long-acting stimulants ($t_{18} = 4.2, P < .0001$). The 2 classes of stimulant medication did not differ significantly from one another ($t_{18} = 1.5, P = .3$). We also found no significant difference between methylphenidate-based and amphetamine-based medications ($t_{11} = 0.1, P = .9$).

[Table 3](#) presents clinical and demographic variables that might potentially confound our meta-analytic comparisons of medication types. We found no significant differences among studies for the distribution of *DSM-IV* subtypes (for studies using *DSM-IV* criteria), gender, or age. [Table 4](#) describes the study design features for the 3 medication classes. We found significant differences for 1 study design feature: short-acting stimulant studies were less likely to use last-observation-carried-forward (LOCF) methodology compared with the

baseline, exclusion of nonresponders, type of score (change score vs outcome score), or study design (crossover vs parallel). There were no significant differences in design features between studies using amphetamine-based medications and those using methylphenidate-based medications.

 [Table 3](#)

Click figure to enlarge

 [Table 4](#)

Click figure to enlarge

We used meta-analysis regression to determine if any of the design features in [Tables 3](#) and [4](#) predicted effect size. Effect sizes were greater for crossover compared with parallel designs (0.88 vs 0.51; $F_{1,19} = 10.0$, $P = .005$), for physician versus self ratings (0.68 vs 0.43; $F_{1,18} = 4.8$, $P = .04$), for outcome compared with change scores (0.75 vs 0.45; $F_{1,18} = 11.4$, $P = .003$), for studies that included prior nonresponders compared with those that did not (0.74 vs 0.36; $F_{1,18} = 7.2$, $P = .0006$), for studies that did not use a placebo lead-in compared with those that did (0.75 vs 0.36; $F_{1,18} = 7.5$, $P = .0006$), for those using completer compared with LOCF methodology (0.91 vs 0.47; $F_{1,18} = 11.3$, $P = .004$), and for those using 1 site compared with multiple sites to enroll subjects (0.83 vs 0.44; $F_{1,18} = 9.8$, $P = .006$). All other effects were nonsignificant (all P values $> .10$). Because use of LOCF methodology was significantly associated with both effect size and drug class, this could explain the observed differences among drug classes. After correcting for this confounding factor, the difference between long-acting stimulants and nonstimulants remained statistically significant

[Figure 4](#) presents the mean NNT for each drug computed across all data points for each drug. Paroxetine is not included in the figure because it had a negative effect size. As described in the Method, the NNT can be computed as a transformation of the standardized mean difference. In this context, a successful outcome means that the outcome of a treated patient is better than it would have been if the patient had not been treated. Thus, higher NNTs correspond to fewer successful treatments. As expected from [Figures 1, 2 and 3](#), [Figure 4](#) shows higher NNTs for all nonstimulants except modafinil and lower NNTs for all stimulants.

[Table 5](#) presents mean effect sizes stratified by the specific outcome scores used by the studies analyzed. It also gives the number of studies that used the outcome score. This table should be interpreted cautiously given that each scale was used by only a handful of studies. Of note, for both stimulants and nonstimulants, effect sizes tend to be higher for the ADHD rating scale.

 [Figure 4](#)

Click figure to enlarge

 [Table 5](#)

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DISCUSSION

Our meta-analysis of efficacy outcomes for medication studies of adults with ADHD found significant differences in effect size between stimulant and nonstimulant medications, even after correcting for study design features that might have confounded the results. This finding and the magnitude of the effect sizes for each drug class were

We found evidence of publication bias for short-acting stimulants, which reduced the mean effect size from 0.96 to 0.86, which is more in line with the effect size for long-acting stimulants (0.73). Although our analyses indicate that effect sizes for stimulants are significantly greater than those for other medications, the presence of confounds suggests that, in the absence of confirmatory head-to-head studies, caution is warranted when comparing the effects of different medications across studies. Although head-to-head trials are needed to make definitive statements about efficacy differences, our results comparing stimulants and nonstimulants are compatible with the efficacy differences from studies of children between atomoxetine and mixed amphetamine salts reported by Wigal et al^{45,46} and the conclusions of a prior review limited to a smaller subset of studies that excluded short-acting stimulants.¹⁸

[Table 1](#) shows little uniformity in the study design parameters used to assess medication efficacy. Although this does not affect the interpretation of individual studies, it makes difficult the comparison of the efficacy of different medications in the absence of direct comparisons within the same study. This problem is further compounded by the fact that effect sizes, which compare treatment efficacy, differ according to some study design variables. Comparing medication effect sizes in different studies, without accounting for these influences, will lead to spurious conclusions. We found that only 1 design variable differed significantly among the medication groups: short-acting stimulant studies were less likely to use LOCF methodology compared with the other types of studies. When we adjusted for this difference using meta-analysis regression, the difference between short-acting stimulants and nonstimulants lost statistical significance.

the 95% confidence interval does not overlap with zero). The only drug that was worse than placebo was paroxetine, which is clearly not effective for ADHD (Figure 3). For the long-acting stimulants (Figure 1) and nonstimulants (Figure 3), heterogeneity within each medication class was not statistically significant. In contrast, for short-acting stimulants, we found evidence of significant heterogeneity among studies. Visual inspection of Figure 2 suggests that the overall pattern of greater dispersion, as compared with Figures 1 and 3, cannot be attributed to 1 or a few extreme study results.

The NNT results (Figure 4) are useful because they give some sense of the clinical implications of the variability of effect sizes among different drugs. For example, some nonstimulants have NNTs approaching 5, and some short- and long-acting stimulants have NNTs near 2. For these more effective stimulants, only 2 patients need to be treated to have 1 positive outcome, compared with 5 patients for the nonstimulants. These NNTs also tell us that for 50% of patients, stimulant trials are wasted (because 1 of the 2 treated patients would have done better or as well on placebo) and for 80% of patients, nonstimulant treatments are wasted. Note that we are using the term “wasted” to mean that the patient would have done as well or better if they had been treated with placebo. The 50% response rate for stimulants and the 20% response rate for nonstimulants are less than response rates reported in the literature because those response rates are not placebo adjusted. Regardless of the absolute magnitude of effect, though, the NNT has implications for both the outcome of individual patients and the costs of wasted treatments. The NNT results also suggest that most patients will need more than 1 drug trial to achieve a positive outcome that cannot be attributed to a placebo effect. Ideally, our NNT result would have been based on a common,

Our work has methodological implications for the design of ADHD treatment studies because several methodological features of the studies were associated with the magnitude of their effect sizes. Physician ratings led to higher effect sizes compared with self ratings. Although self-ratings may be sufficiently reliable and sensitive in some contexts, they do not appear to be as useful as physician ratings for detecting response to ADHD medications. Studies using outcome scores had higher effect sizes than studies using change scores. The use of change scores may be more conservative because they adjust for baseline group differences. Crossover designs had greater effect sizes than parallel designs; this finding makes sense given the inherent matching in the crossover design that removes between-patient variability from the analysis. Studies using only 1 site had greater effect sizes than studies using multiple sites. This may be due to difficulties managing large multisite trials, especially as regards standardization of methods. As expected, studies using the conservative LOCF methodology had smaller effect sizes than studies that used only completers in the analysis. Of note, all of the multisite trials used LOCF methodology.

It is difficult to compare the short- and long-acting stimulants because the studies we reviewed were not intended to assess the duration of the effect of a medication throughout the day. Moreover, the use of short-acting medications in a clinical trial environment may not reflect the real-world effects of missed doses if compliance is enhanced by the clinical trial. In contrast to our conclusions, Peterson and colleagues' ²⁰ meta-analysis of medication studies of adult ADHD found that short-acting stimulants were more effective than long-acting stimulants. Although our initial analysis showed short-acting stimulants to have greater effect sizes than long-acting stimulants, that difference could be accounted for by study confounds and

stimulant studies. For example, all of the long-acting studies used conservative LOCF methodology, compared with only 15% of the short-acting studies. There are 3 other differences between our study and the study by Peterson et al,²⁰ which may explain differences in results: (1) we excluded studies of substance abusers, whereas they did not; (2) we used continuous measures of ADHD outcomes, whereas they used the proportion of responders; and (3) we included Biederman and colleagues' ⁴⁷ study of LDX, which was previously unavailable to Peterson et al but which also had the highest effect size among the long-acting stimulants.

Our work must be interpreted in light of several limitations. Compared with studies of child and adolescent ADHD, there are relatively few treatment studies of adult ADHD. And because meta-analysis relies on data collected by others, the validity and strength of our conclusions rely on the quality of the individual studies, which was beyond our control. Although our inclusion criteria required each study to meet criteria for study quality (use of double-blind placebo-controlled methods, selection of subjects with structured diagnostic criteria), other features of these studies may account for some of the interstudy variability in results. Because we relied on data presented by authors, we could not assess the effects of all potential confounds; ie, we were limited by what other investigators chose to present. For example, we could not compute the effect sizes at specific time points, because such data were rarely provided. Similarly, we did not assess differential duration of action between medication classes, because this effect is rarely presented. Our conclusions about short-acting stimulants are limited by the significant heterogeneity we found for their effect sizes. All meta-analyses are limited by the quality of the studies analyzed. For that reason, we limited our review to double-blind placebo-

differences between drugs or classes of drugs might have led to spurious results.

Our meta-analysis excluded studies not meeting our inclusion criteria. We excluded 2 open trials. One reported a 70% response rate using doses of 40 mg/d.⁴⁸ We excluded a double-blind parallel study by Wood et al⁴⁹ because they did not use structured diagnostic criteria. Instead, they used the diagnosis of minimal brain dysfunction to select patients for study. Using a low mean dose of 27 mg/d, they found a 53% improvement rate in methylphenidate-treated adults with minimal brain dysfunction. We excluded Iaboni and colleagues'⁵⁰ double-blind crossover study because it did not provide the data needed to compute an effect size. We also excluded studies that did not provide data to compute the SMD⁵¹ or that only provided data on ADHD patients with substance use disorders.⁵²⁻⁵⁸

Although indirectly comparing treatments using meta-analysis cannot replace direct comparison of treatments within the same study, there is evidence from other medical fields that meta-analysis is a valid approach. Song et al⁵⁹ examined 44 published meta-analyses that used measures of effect magnitude to indirectly compare treatments. In most cases, the results using indirect meta-analysis comparisons did not differ from the results of direct comparisons within the same study. However, for 3 of the 44 comparisons, they found significant differences between the direct and the indirect estimates. Chou et al⁶⁰ compared initial highly active antiretroviral therapy (HAART) with a protease inhibitor (PI) versus a nonnucleoside reverse transcriptase inhibitor (NNRTI). They did a direct meta-analysis of 12 head-to-head comparisons and an indirect meta-analysis of 6 trials of NNRTI-based HAART and 8 trials of PI-based HAART. In the direct meta-analysis

suppression. From these studies, it seems reasonable to conclude that indirect comparisons usually agree with the results of head-to-head direct comparisons. Nevertheless, when direct comparisons are lacking, the results of indirect comparisons using measures of effect magnitude should be viewed cautiously.

Despite these limitations, our findings highlight the remarkable variability in methods among adult ADHD treatment studies. Although this does not argue against the validity of individual studies, it highlights the difficulty one faces when interpreting differential medication efficacy when a direct comparative trial is not available. Yet, despite this variability, we found substantial and significant differences in efficacy between stimulant and nonstimulant medications. Although efficacy effect sizes should not be the sole guide for clinicians to use when choosing an ADHD medication, they do provide useful information for clinicians to consider when planning treatment regimens for patients with ADHD.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin, Aplenzin, and others), clonidine (Catapres, Jenloga, and others), dexamethylphenidate extended release (Focalin XR), dextroamphetamine (Dexedrine, Dextroamp, and others), guanfacine (Intuniv, Tenex, and others), lisdexamfetamine dimesylate (Vyvanse), methylphenidate (Ritalin, Daytrana, and others), mixed amphetamine salts (Adderall), modafinil (Provigil), osmotic-release oral system methylphenidate (Concerta), paroxetine (Paxil, Pexeva, and others).

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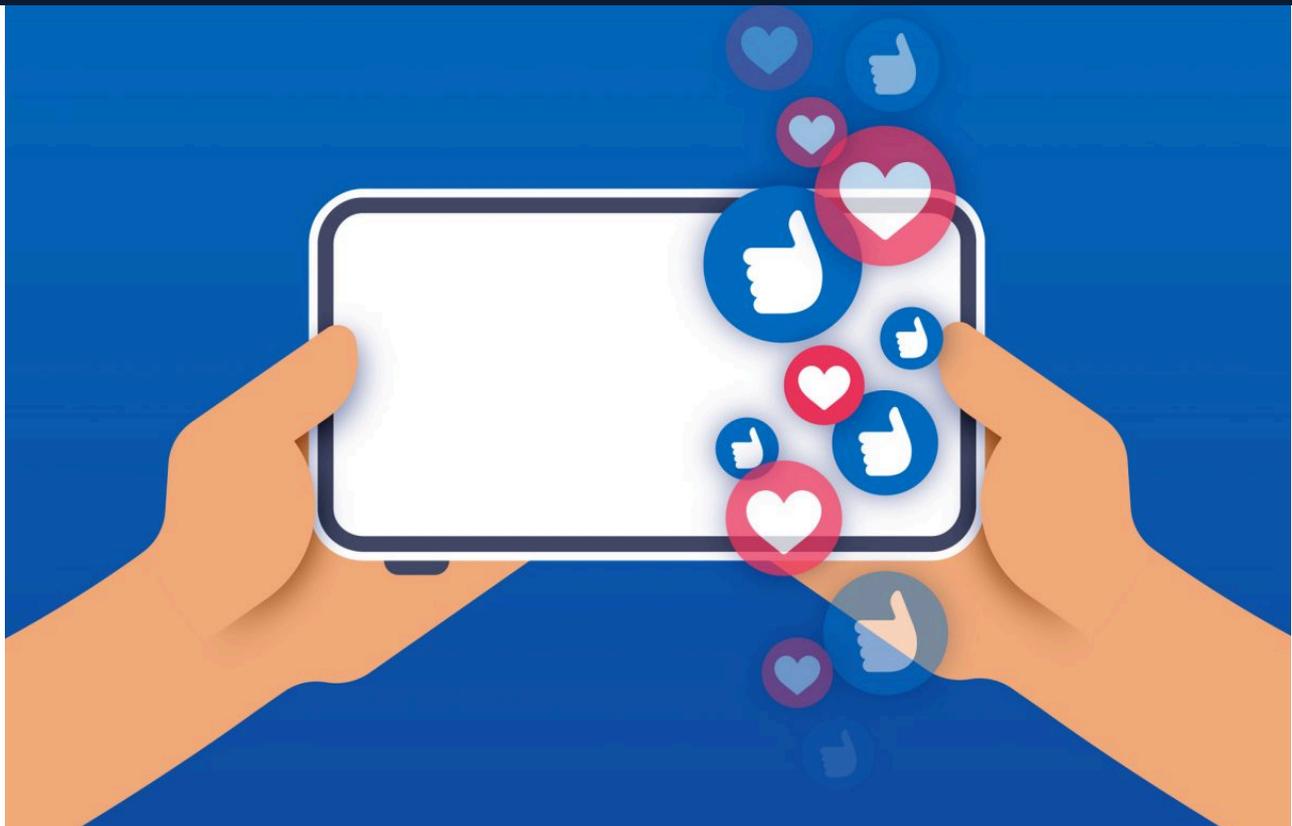
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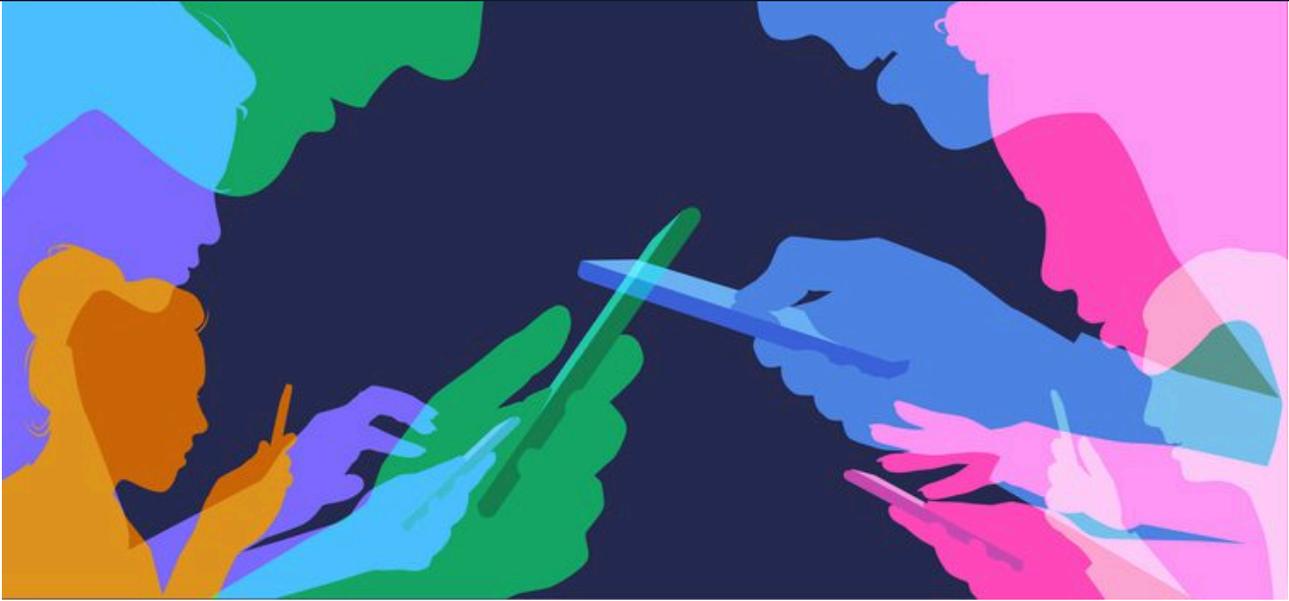
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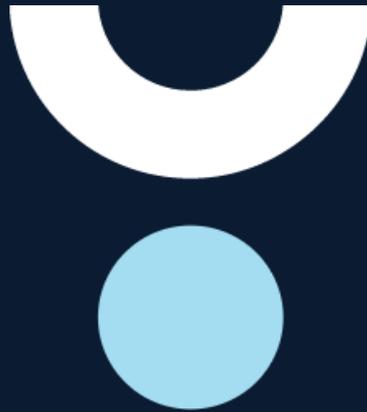
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