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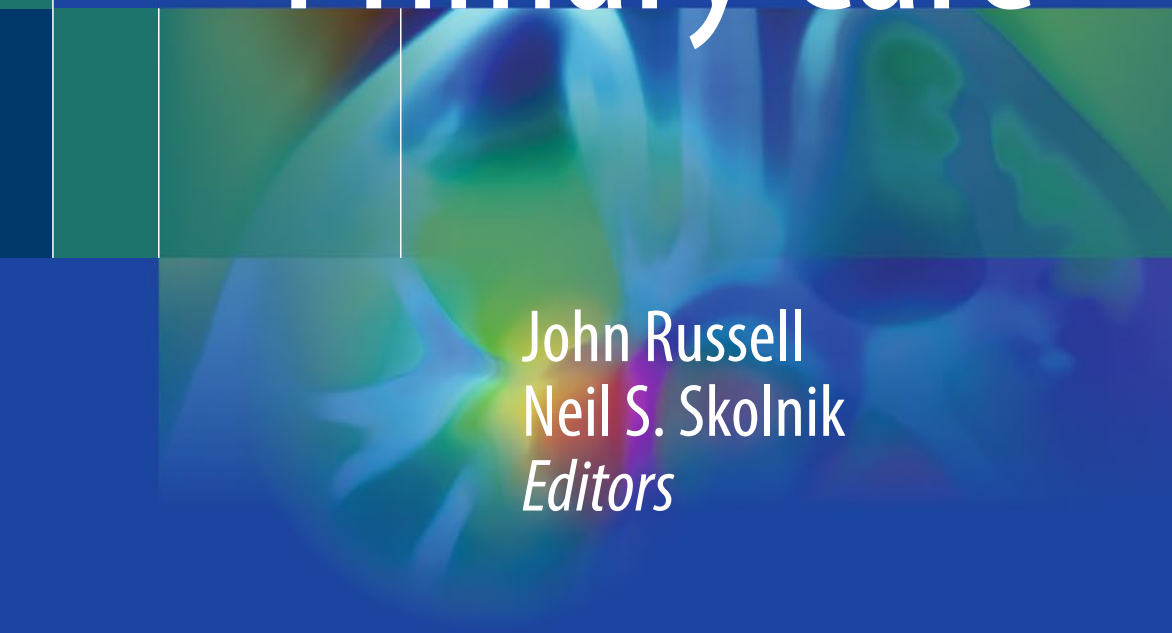

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John thanks

Elena, Dana, Erin and Paul

for all their love and support

Neil thanks

Alison, Aaron and Ava

who give life meaning, love and purpose

John and Neil would both like to thank

thirty years of residents who inspire our teaching

and who have taught us more than we taught them.

"We stand on the shoulders of giants"

Introduction

The two of us have worked together in the Abington Family Medicine Residency Program for over thirty years. During that time, we have learned more, argued more, joked more, and just had more fun together and with our colleagues than any two people should to be allowed to have over the course of a career. All the time with unending respect for each other's intellect, empathy and humor.

We've taken care of patients and we've taught patient care.

Most relevant to this project, we've shared a love of ideas and the medical literature, and how that literature can be applied to patient care.

All of this is the backstory to this book—a love of the medical literature and a belief that an understanding and appreciation of that literature can enhance our lives as physicians, as well as the lives of our residents, students and patients.

We know that there is no one right answer to what are the top articles in primary care. All of us have our favorites, and inevitably there will be articles here that you will think should not have been included in such esteemed company, and you will have favorites that have been left out. This book will always be a work in progress, it has to be. There is a good chance that a new top article describing a critically important discovery for patients may come out next week. Don't hesitate to let us know if there is an article that you feel should be in here which was not, we'll seriously consider it for our next edition.

We want to take this opportunity to thank a hospital system that supports an academic community hospital family medicine residency and encourages intellectual pursuits, individual growth, innovation and learning.

We also want to thank seven very special individuals—the faculty at Abington Family Medicine—many of whom joined us in this project and with whom we daily share the joys and frustrations of academics, teaching and patient care—Gerald "Trip" Hansen, Mathew Clark, Amy Clouse, Tracey Roesing, Susan Kuchera Fidler, Meera Shah, and Bill Callahan.

Finally, we want to thank our families, who make it all worthwhile and who support us and put up with the sacrifices that a life in academic family medicine entails.

Deepest thanks, from John, to Elena, Dana, Erin, and Paul. Deepest thanks, from Neil, to Alison, Aaron and Ava. We (humbly) feel we have learned so much from each member of our family.

And…ok…thanks to each other.

~~Neil and John~~ John and Neil

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Part I
Behavioral Health

Aaron Sutton

Chapter 1
Treatment Strategies in ADD-1999

Mackenzie Kramer

Background

Attention-deficit hyperactivity disorder (ADHD) is defined by the DSM-V as a persistent pattern of inattention and/or hyperactivity/impulsivity that interferes with functioning and development [1]. ADHD is the most common psychiatric disorder in childhood, affecting 3–5% of school aged children and accounting for 30–50% of child referrals to mental health services [2, 3]. Previous studies have showed the efficacy of short-term treatments of both pharmacotherapy and behavior therapy in treating symptoms of ADHD; however, few controlled studies have followed participants for greater than four months. At the time this study was undertaken, there was a great deal of public concern over the use of stimulants in children with ADHD given the lack of evidence to show that they are effective. This study, the Multimodal Treatment Study of Children With ADHD (MTA), aimed to evaluate pharmacotherapy, behavior therapy, and a combination of the two in a longer-term clinical trial.

The MTA Cooperative Group. A 14-Month Randomized Clinical Trial of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder. Arch Gen Psychiatry. 1999;56(12):1073–1086. doi:10.1001/archpsyc.56.12.1073. https://jamanetwork.com/journals/jamapsychiatry/fullarticle/205525

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Objective

- To see how long-term medication and behavioral treatments compare with one another when treating children with ADHD, and if there is an additional advantage to using these treatment modalities in combination.
- To evaluate the effectiveness of carefully delivered treatments against routine community care.

Design and Methods

- The study included 579 children, aged 7–9.9 years, with ADHD Combined Type who were randomly assigned to one of the four treatment groups for 14 months.
- Outcomes were measured in distinct groups rated by parents and teachers: primary ADHD symptoms, aggressive and oppositional behavior, internalizing symptoms, for example, anxiety and sadness, social skills, parent–child relationship, and academic achievement.
- Treatment groups included intensive medication management alone, intensive behavioral treatment alone, a combination of both, and routine community care (the control group).
- Behavioral treatment included parent, school, and child components with therapist involvement that gradually reduced over time.
- Medication management was with methylphenidate hydrochloride. If adequate response to methylphenidate was not obtained during titration, alternate medications were titrated openly in the order until a satisfactory response was found: dextroamphetamine, pemoline, imipramine, and, if necessary, others approved by a cross-site panel. Eighty-nine percent completed titration of medication; of these, Sixty-nine percent were assigned to an individually titrated dose of methylphenidate, with average initial doses of 30.5 mg/d. The remaining subjects were openly titrated to dextroamphetamine due to inadequate response to methylphenidate.
- Standard community care involved treatment by community providers. It should be noted that the community care group included many children who received medication and behavioral therapy, since a placebo group with no intervention would have been unethical for this disorder over this period of time.
- Data was analyzed by intent-to-treat random-effects regression procedures over a course of 14 months.

Results

- All 4 groups showed sizable reduction in ADHD symptoms over time, with significant differences between the groups in the degree of improvement.

- Medication management alone, when compared to behavioral treatment alone, showed significant improvements in primary ADHD symptoms, including inattention and hyperactivity-impulsivity, rated by parents and teachers. According to the authors, "Robust differences were found according to 2 different data sources, indicating the superiority of medication management over behavioral treatment for ADHD symptoms."
- When comparing other areas of children's functioning including aggressive and oppositional behavior, peer relations, and academic achievement, medication management alone showed no significant benefit when compared to behavioral treatment alone.
- Children in the combined treatment group and the medication management group showed significant improvement compared to those in the behavioral treatment group as well as the control group. Combined treatment and medication management did not differ significantly across any domain.
- Combined treatment and medication management were superior to community care for parent- and teacher-reported ADHD symptoms. Behavioral treatment showed no significant benefit compared to community care.

Importance

ADHD is the most common psychiatric disorder in childhood and has now been seen to persist into adulthood. This study was the first of its kind to evaluate the differences between pharmacotherapy, behavioral therapy, and a combination of the two in a longer-term clinical trial. While all groups showed a reduction in ADHD symptoms over time, there were important benefits to medication, as well as combined medication and behavioral treatment, with no significant effect of behavioral treatment alone. The MTA updates, which are published approximately every 2 years, give us an insight into more long-term health effects of medication, efficacy, and more research that needs to be done.

Updates

- The MTA was designed and conducted in the early 1990s and underwent eight assessments from the baseline data, published every 2 years.
- In 2007, the MTA published a follow-up following 485 of the original 579 children. Among children who continued to take the ADHD medication consistently, the stimulants started to lose effectiveness around three years after treatment was started [2].
- At the 16-year follow up, it was concluded that more than 60% of children, regardless of their medication use, continued to show ADHD symptoms into adulthood [4, 5].

- Multiple studies have shown strong evidence for decreased height associated with prolonged psychostimulant medication taken consistently compared to those who stopped stimulant medication or took it sporadically[5].

Bottom Line

- While all four groups showed improvement over time medication management and combined medication and behavioral therapy were superior to behavioral treatment or community treatment in reducing ADHD symptoms.
- Combined treatment was not better than medication alone for reducing core symptoms of ADHD.
- The authors point out the lack of efficacy of behavioral treatments on the core ADHD symptoms does not mean that behavioral therapy is not important and does not help critical domains of function. ADHD is a chronic disease, the manifestations of which wax and wane over time, often depending upon demands and stressors. Behavioral therapy has values in helping to function optimally given those many issues.
- The original data published in 1999, as well as the extensive follow-up data over the following 16 years, show that an optimal dose of stimulant medication provides children with ADHD an effective way to improve symptoms; however, over time, the medication loses effectiveness.
- The MTA findings challenged the notion that 50% of children with ADHD outgrow the disorder in adulthood. Although intermittent periods of remissions can be expected, approximately 90% of participants in the MTA trial experienced residual ADHD symptoms in young adulthood [6].
- Clinicians must work with their patients to develop an individualized plan for treatment of ADHD and carefully monitor medication prescribed at the correct dose while utilizing other interventions including behavioral therapy.

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Chapter 2
Cognitive Behavioral Therapy Versus Medications in Depression-2005

Christian Iversen

Background

Both medications and cognitive therapy had shown efficacy in treatment of depression, including a large study by the Treatment of Depression Collaborative Research Program (TDCRP). This research demonstrated medications were superior to cognitive therapy for severe depression which became the standard of care recommended by the American Psychiatric Association. Prior to this study, there was no randomized, placebo-controlled comparison of medication and cognitive therapy for treatment of moderate to severe depression.

Objective

- To compare efficacy of antidepressant medication and cognitive therapy for treatment of moderate to severe depression.

DeRubeis, R. J., Hollon, S. D., Amsterdam, J. D., Shelton, R. C., Young, P. R., Salomon, R. M., O'Reardon, J. P., Lovett, M. L., Gladis, M. M., Brown, L. L., & Gallop, R. (2005). Cognitive therapy vs medications in the treatment of moderate to severe depression. *Archives of general psychiatry, 62(4),* 409–416. https://doi.org/10.1001/archpsyc.62.4.409. https://jamanetwork.com/journals/jamapsychiatry/fullarticle/208460

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Design and Methods

- Participants had a diagnosis of major depressive disorder according to DSM IV, were 18–70 years old, spoke English, and could provide informed consent.
- Patients were assessed by the 17-question Hamilton Depression Rating Scale (HDRS) modified to account for both typical and atypical presentations of depression. Patients were required to score 20 or more on two occasions separated by 7 days, and diagnosis was confirmed by a psychiatrist.
- Eligible patients were randomly assigned to medication (n = 120), placebo pill (n = 60), or cognitive therapy (n = 60). Placebo pills were only used for 8 weeks. The medication group was larger to allow additional randomization at the conclusion of this study to assess relapse [1].
- Pharmacology group (paroxetine and placebo pill):
  - Pharmacotherapy sessions conducted by psychiatrists to discuss medications and provide limited supportive counseling. Cognitive therapy techniques were prohibited.
  - Paroxetine doses started at 10–20 mg/day and increased to maximum of 50 mg/day.
  - Patients who failed to respond to paroxetine by 8 weeks were offered additional treatment.
  - Blinding for patients and psychiatrists of the placebo group was broken at 8 weeks, and treatment was offered.
- Cognitive therapy group:
  - Psychologists and a psychiatric nurse practitioner conducted cognitive therapy sessions.
  - Patients were initially treated with 50-min sessions biweekly for 4 weeks with progression to weekly sessions over the subsequent 12 weeks.
- Outcome analysis:
  - The primary endpoint was HDRS reduction at 8 and 16 weeks, with response indicated by a score of 12 or less and stable or decreasing levels at the end of the study.
  - Full remission was defined as HDRS of 7 or less.

Results

- There was nearly equivalent attrition in both medication and cognitive therapy groups. Notably, 5% of the medication group stopped due to side effects or worsening symptoms; approximately 7% stopped therapy for dissatisfaction.
- Paroxetine dose started at 14.0 ± 4.9 mg rising to 37.3 ± 12.4 mg at the end of 16 weeks.

- 47 patients (39%) required augmentation of therapy with lithium, desipramine, venlafaxine, or some combination thereof due to insufficient response on HDRS.
- Both medication and cognitive therapy outperformed placebo to a statistically significant level at 8 weeks. At this point, placebo treatment was discontinued.
- There was no statistically significant difference between medication and cognitive therapy for response rates at 8 or 16 weeks, or for remission at 16 weeks.
- There was evidence that patients with comorbid anxiety responded better to medication, "perhaps because paroxetine […] has anxiolytic effects".
- There was additional evidence that cognitive therapy at Pennsylvania was more effective than Vanderbilt, "likely related to therapist experience'.

Importance

Similar efficacy was demonstrated for both cognitive therapy and medication for symptomatic improvement and remission of moderate to severe depression in this randomized, placebo-controlled trial. Both treatments were superior to placebo pill. This study provided additional evidence for the therapeutic value of both cognitive therapy and medication management of depression.

Updates

- Patients were followed to assess rates of relapse following completion of the above study [1]. Patients withdrawn from cognitive therapy were less likely to relapse compared with those withdrawn from medication. There was no statistical difference between those withdrawn from therapy and those continuing medication.
- The American Psychiatric Association (APA) recommends second generation antidepressants (SSRI or SNRI), cognitive therapy, or a combination thereof for initial treatment of depression in adults [2]. They additionally suggest cognitive therapy to prevent relapse following remission.

Bottom Line

- Both medication and cognitive therapy provided therapeutic benefit for patients experiencing moderate to severe depression. Relapse was more common following discontinuation of medication compared with therapy. Importantly, therapist experience likely influenced outcomes.

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Chapter 3
Treatment for Major Depressive Disorder (STAR*D)-2008

Aaron M. Sutton

Background

Depression affects approximately 1 in 8 Americans and is the second leading cause of disability-adjusted life years in those 15–44 years old [1]. The majority of individuals with major depressive disorder (MDD) have a chronic or recurrent course and many continue to have symptoms and periods of disability between episodes [2]. Prior to the Sequenced Treatment Alternative to Relieve Depression (STAR*D) trial, there was little evidence in regard to treating patients in real world settings. The majority of previous trials included participants who were recruited through advertisement and who often had few medical or psychiatric comorbidities. In addition, though there had been many trials of the effectiveness of antidepressants in patients with MDD, there was not much evidence about additional anti-depressive treatment that is often needed for the large proportion of patients (up to two-third of patients) who do not respond, or have only a partial response, to first line treatment.

Warden, Diane & Rush, Augustus & Trivedi, Madhukar & Fava, Maurizio & Wisniewski, Stephen. (2008). The STAR*D Project results: A comprehensive review of findings. Current psychiatry reports. 9. 449-59. 10.1007/s11920-007-0061-3. https://link.springer.com/article/10.1007/s11920-007-0061-3

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Objective

The STAR*D trial aimed to develop treatment strategies that would improve clinical outcomes in patients with treatment resistant depression, who were experiencing a major depressive episode. Specifically, the trial focused on how to initiate treatment and what the next steps in treatment would be, should participants not reach remission or cannot tolerate the treatment.

Design and Methods

- Over a 7-year period, 4041 outpatients between 18 and 75 years of age were enrolled from 41 clinical sites across the country; 2876 were eligible and began level 1. Level 2 results included 1439, level 3 included 377, and level 4 included 142.
- In level 1, participants were given citalopram (Celexa) for 12–14 weeks. If patients became symptom free, they could move to a 12-month follow-up program in which Celexa was continued and patients were monitored. If participants could not tolerate Celexa, or did not become symptom free, they moved to level 2.
- Participants in level 2 had the option of switching medication or adding medication to Celexa. Those who switched were randomly assigned either sertraline (Zoloft), bupropion-SR (Wellbutrin), or Venlafaxine XR (Effexor). If augmenting, participants were randomly assigned bupropion-SR (Wellbutrin) or buspirone to continue with Celexa. Participants also had the option of adding on or switching to cognitive therapy. As in level 1, if participants became symptom free, they would continue with treatment and those who did not or could not tolerate treatment moved to level 3.
- Level 3, like level 2, allowed participants the opportunity to switch or augment. If switching, participants were randomly assigned either mirtazapine (Remeron) or nortriptyline (Aventyl or Pamelor) for up to 14 weeks. In the augmentation group, participants were randomly assigned to lithium or triiodothyronine (T3). As in previous levels, if participants became symptom free, they would be monitored and those who did not or could not tolerate medications proceeded to level 4.
- Participants in level 4 were taken off any previous medications and randomly switched to either the monoamine oxidase inhibitor (MAOI) tranylcypromine (Parnate) or the combination of venlafaxine extended release (Effexor XR) with mirtazapine (Remeron).

Results

- The majority of clinical trials for depression use a measure of success called "response," which means that symptoms have decreased to at least half of what they were when starting a trial. However, the STAR*D trial uses the measure of remission, meaning that participants were symptom free, however notates response as well.
- In level 1, remission rates were between 28 and 33% with further response rate between 10 and 15% depending on what measurement was used for assessment, either the Hamilton Depression Rating Scale (HDRS) or Quick Inventory for Depression Screening (QIDS).
- At level 2, patients who did not have a full response to citalopram were switched to either bupropion-SR, sertraline, and venlafaxine-XR. About one-fourth of patients who had a medication switch experienced a remission, and remission rates for bupropion-SR, sertraline, and venlafaxine-XR were similar.
- At level 2 patients could choose augmentation with bupropion-SR or buspirone. Patients treated with bupropion-SR showed greater symptom improvement, lower symptom severity, and fewer dropouts due to intolerance.
- Cognitive therapy had equal efficacy when used as a level 2 augmentation strategy as when medication was used to augment citalopram. When used as "switch therapy," i.e., when patients stopped their level 1 citalopram therapy and switched to either a different medicine or cognitive therapy, a fourth of patients had equal efficacy to switching medications, with approximately a fourth of patients in both groups showing a response.
- Level 3 remission rates varied between switching to mirtazapine (12%) and augmentation with triiodothyronine or T3 (25%). Again, there were no statistically significant differences in medications used.
- In level 4, the remission rate from switching to tranylcypromine was 7%, while the combination of venlafaxine extended release (Effexor XR) with mirtazapine (Remeron) was 14%.

Importance

With an estimated 16 million Americans experiencing a depressive episode in a given year, family physicians are on the front line of providing care. Currently, general practitioners prescribe about 60% of all psychotropic medications with family medicine physicians being a majority in that group [3]. It is important to understand all treatment options including how to initiate treatment, augmenting treatment, providing options and rationale for psychotherapy, and discussing expectations for treatment with patients.

Updates

- Multiple articles have been published since the results of STAR*D were published asking for further evaluation of results based on biases. Potential detriments to the study include "treat to remission method," overstated estimates of remission, acknowledgement of participants that dropped out through step 3, and an assumption that those who dropped out could be included in the group that was successfully treated [4].

Bottom Line

- Primary care physicians can effectively treat depression in a primary care "real world" setting. Many patients who do not achieve remission or response after a few weeks typically do so after 14 weeks. If initial treatment with an SSRI does not lead to full remission, the evidence supports additional therapeutic approaches. The therapeutic approach can be effective in leading to remission either by switching to a different anti-depressant, or by augmenting the initial treatment with bupropion-SR. Cognitive therapy had efficacy equal to medication as second level therapy either by switching to cognitive therapy or augmenting the existent medication with cognitive therapy.

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