# Do insulin-sensitizing drugs increase ovulation rates for women with PCOS?

## EVIDENCE-BASED ANSWER

Short-term use of metformin (Glucophage) improves ovulation rates for women with polycystic ovary syndrome (PCOS) (strength of recommendation [SOR]: **A,** based on systematic reviews of randomized controlled trials [RCT]). Metformin also decreases menstrual irregularities (SOR: **B,** extrapolated from a systematic review). When added to clomiphene, metformin increases ovulation and pregnancy rates when compared with clomiphene alone (SOR: **A**, systematic review).

Thiazolidinediones (TZDs) improve ovulation rates as well (SOR: **B,** based on low-quality RCTs). Research of longer duration including the key outcomes of pregnancy and birth rates, is needed to clarify the appropriate use of insulin-sensitizing drugs for PCOS.

## EVIDENCE-BASED SUMMARY

A common female endocrinopathy, PCOS affects 5% to 10% of women. Characterized by anovulation and hyperandrogenism, it often manifests as infertility and irregular menstruation. Metformin and thiazolidinediones are likely effective treatments for these expressions of insulin resistance, but study limitations restrict our ability to clearly define their role.

The most influential systematic review was a meta-analysis that reviewed 13 RCTs including 543 women to determine the effects of metformin on ovarian function in PCOS.[1,2] By selecting RCTs, performing precise statistical analysis according to the Cochrane protocols, and clearly stating limitations, this review gives good evidence that metformin modestly increases the odds of ovulation for women with PCOS (odds ratio [OR]=3.88; 95% confidence interval [CI], 2.25–6.69 for metformin vs placebo) and that metformin with clomiphene (Clomid) effectively increases ovulation (OR=4.41; 95% CI, 2.37–8.22) and pregnancy rates (OR=4.40; 95% CI, 1.96–9.85) when compared with clomiphene use alone. When metformin is used as a sole agent, ovulation is achieved in 46% of recipients compared with 24% in the placebo arm (number needed to treat [NNT]=4.4). When metformin and clomiphene are

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## What are Clinical Inquiries?

**Clinical Inquiries** answer recent questions from the practices of family physicians. Practicing family physicians choose the most relevant questions submitted through a web-based voting system operated by the Family Physicians Inquiries Network (FPIN; online at www.fpin.org).

FPIN is national, not-for-profit consortium of family medicine departments, community residency programs, academic health sciences libraries, primary care practice-based research networks, and other specialists. Once questions are selected, FPIN editors then organize teams of clinicians and librarians to answer them based on systematic review of the world literature.

Answers are developed through an explicit, systematic method:

- FPIN librarians and editors identify questions recently answered in best evidence sources (e.g. Cochrane Reviews, Clinical Evidence, the US Preventive Services Task Force, Evidence Based Guidelines, a published systematic review).
- FPIN librarians then conduct systematic and standardized literature searches of best evidence sources, Medline, and other databases in collaboration with an FPIN clinician or clinicians. If a best evidence source has been identified, the search begins from the date of the search conducted for that source. Otherwise, the searches are comprehensive.
- FPIN clinician authors then choose the highest quality original research sources, and critically appraise the research and integrate the findings in the Evidence Based Answer and Evidence Summary section of Clinical Inquiries. Authoritative sources are also quoted in the "Recommendations from Others" section of the Clinical Inquiry.
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used in combination, 76% of recipients ovulate compared with 42% receiving clomiphene alone (NNT=3.0).

Several problems with recommending metformin as first-line therapy exist: (1) equal or better ovulation rates have been described by using lifestyle interventions to achieve weight loss, (2) there are no long-term studies of the effects of metformin in PCOS patients, and (3) we cannot assess the clinically important outcome of pregnancy rates because the trials did not control for other infertility factors and did not define live births as a primary outcome. In addition, there are no head-to-head trials of metformin vs clomiphene, the standard first-line therapy for ovulation induction. Only 1 study addressed menstrual patterns specifically; they were improved with metformin (OR=12.88; 95% CI, 1.85–89.61).

An additional meta-analysis reports similar results.[3] Eight RCTs addressing the use of metformin or clomiphene for treatment of PCOS were reviewed for ovulation and pregnancy rates. Metformin is 50% better than placebo for ovulation induction among infertile PCOS patients (relative risk [RR]=1.50; 95% CI, 1.31–1.99), but this benefit is not necessarily improved with longer duration (>3 months) of therapy (RR=1.37; 95% CI, 1.05–1.79). Also, metformin is beneficial in regulating cycles for fertile PCOS patients with irregular menses (RR=1.45; 95% CI, 1.11–1.90).

The conclusions regarding pregnancy rates and combined therapy with metformin and clomiphene are limited due to small samples, short follow-up time (2–6 months), and study design. An ongoing randomized trial (Pregnancy in Polycystic Ovarian Syndrome: PPOS study) of 768 infertile PCOS patients is investigating effects of metformin vs clomiphene on ovulation induction and achievement of singleton pregnancies. These outcomes should clarify remaining uncertainties regarding appropriate use of metformin.

Finally, a review of 7 RCTs describes the evidence accumulated by well-designed trials and its clinical relevance.[4] Metformin improves ovulation and menstrual cyclicity but these improvements were variable and modest. On average, 1 additional ovulation is attained in every 5-month interval with metformin treatment; specifically, the baseline of 1 ovulation per 5-month interval increased to 2 ovulations per 5-month interval. Spontaneous ovulation and normal menstruation are achieved rapidly (within 3 months of the start of therapy). These data corroborate the benefits of metformin but place its clinical significance in perspective. For PCOS patients seeking cycle regulation but not pregnancy, oral contraceptives may remain better therapy because metformin does not normalize menses.

**For PCOS patients seeking cycle regulation, oral contraceptives may remain the better therapy**

Less information exists on the role of TZDs and ovarian function in PCOS. Studies of the most researched drug in the class, troglitazone (Rezulin), report improvements in ovulation rates and metabolic markers of PCOS.[5,6] Troglitazone has been taken off of the market due to hepatotoxicity, but results from a RCT of 40 patients with PCOS reported that the use of pioglitazone (Actos) for 3 months increased normal regular cycles and ovulations over placebo (41.2% vs 5.6%; $P<.02$).[7] No liver effects were noted, but caution must be taken since these drugs are pregnancy class C. Two small RCTs studied the use of rosiglitazone (Avandia) in combination with clomiphene and reported improvements in menstrual regularity[8] (92% with combination therapy achieved improved menstrual cycles vs 68% with rosiglitazone alone; OR=0.185) and both spontaneous and clomiphene-induced ovulation rates (52% of clomiphene-resistant women ovulated after rosiglitazone therapy and 77% vs 33% ovulated with combination therapy vs rosiglitazone alone, $P=.04$).[9] Further research is needed to determine the clinical effects of the thiazolidinediones.

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## RECOMMENDATIONS FROM OTHERS

The American College of Obstetricians and Gynecologists guideline on diagnosis and management of PCOS reports that interventions that improve insulin sensitivity, including weight loss, use of metformin, and use of TZDs are useful for improving ovulatory frequency for women with PCOS.[10] The recommendation is based on good and consistent scientific evidence (SOR: **A**). They also note that insulin-sensitizing agents may improve many risk factors for diabetes and cardiovascular disease, but this recommendation is based on limited evidence (SOR: **B**). Finally, they recommend, based on expert opinion (SOR: **C**), that caution be used with these agents because their effects on early pregnancy are unknown, even though metformin appears to be safe.

The American Association of Clinical Endocrinologists recommends using metformin 850 mg twice daily to treat the hyperandrogenic state of PCOS.[11] The use of TZDs is less clear due to limited evidence and risks of teratogenicity.

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## CLINICAL COMMENTARY

### For those trying to conceive, the tried-and-true medication is clomiphene

I tend to think of women with PCOS as falling into 2 camps, those actively trying to conceive and those who are not. Those who are not can often get benefits for their menstrual cycles and hyperandrogenism with birth control pills. For those trying to conceive, the tried-and-true first-line medication is clomiphene.

Metformin has been figuring prominently in the literature as adjunct or second-line therapy for infertility for women with PCOS. It is also an accepted treatment for hirsutism. So, for women with PCOS, metformin is a treatment that bridges the 2 camps. I look forward to seeing head-to-head trials of metformin, clomiphene, and both therapies for induction of ovulation.

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# What are effective treatments for oppositional and defiant behaviors in preadolescents?

## EVIDENCE-BASED ANSWER

Parent training is effective for treating oppositional and defiant behaviors (strength of recommendation [SOR]: **A**, based on systematic reviews). Parent training programs are standardized, short-term interventions that teach parents specialized strategies—including positive attending, ignoring, the effective use of rewards and punishments, token economies, and time out—to address clinically significant behavior problems. In addition to parent training, other psychosocial interventions (**Table**) are efficacious in treating oppositional and defiant behavior.

To date, no studies have assessed the efficacy of medication in treating children with pure oppositional defiant disorder (ODD). However, studies have shown amphetamines to be effective for children with ODD and comorbid attention deficit/hyperactivity disorder (ADHD) (SOR: **A**, based on a meta-analysis).

## EVIDENCE SUMMARY

Oppositional and defiant behaviors include noncompliance, temper tantrums, arguing, and mild aggression. Children exhibiting these behaviors may have a diagnosis of ODD. Importantly, this review does not examine treatments for children diagnosed with conduct disorder or those exhibiting more deviant behaviors such as serious aggression and delinquency.

Eight well-done systematic reviews examined the effectiveness of parent training programs. Parent training is typically conducted by clinical child psychologists but may also be available through certified parenting educators (see the National Parenting Education Network web page for links to state organizations, at www.ces.ncsu.edu/depts/fcs/npen/). Parent training strategies are also described for parents in books such as *Your Defiant Child.*[1]

The most rigorous of the reviews looked at 16 randomized controlled trials that examined the effectiveness of training programs for children between the ages of 3 and 10 years who had "externalizing problems," including temper tantrums, aggression, and noncompliance.[2] All studies included in the review compared a group-based parent training program with a no-treatment wait-list control group and assessed outcomes using a standardized measure of behavior. In studies where sufficient data were provided, effect sizes ranged from 0.6 to 2.9. This indicates that, on a standardized child behavioral measure, parental report of children's externalizing problems decreased by 0.6 to 2.9 standard deviations from pre- to posttreatment (an effect size of >0.8 is considered large). In the 2 studies that included independent observations of child behavior, the benefits reported by parents were confirmed by these observations.

Although parent training has the strongest evidence as a treatment for oppositional and defiant behavior, other psychosocial treatment interventions have been found by multiple randomized controlled trials to be superior to no treatment or wait-list controls (**Table**).

In treating oppositional behaviors among children with ADHD and comorbid oppositional defiant disorder or conduct disorder, a meta-analysis identified 28 studies of children age 7 to 15 years that addressed oppositional/aggression-related behaviors within the context of ADHD.[8] The analysis found that stimulants are efficacious. The overall weighted effect size (a measure of improvement representing the average effects across all reporters) was 0.89. This indicates that raters saw a change in oppositional behaviors—noncompliance, irritability, and temper tantrums—that

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TABLE

## Additional ODD treatments supported by randomized controlled trials

| Treatment and representative study | Treatment description | Outcome |
|---|---|---|
| Anger Coping Therapy[3]<br><br>SOR: **B** | A 12- to 18-session group cognitive-behavioral and social problem-solving training program. Assessed independently (AC) and with a teacher component (ACTC) | AC and ACTC exhibited reductions in directly observed disruptive and aggressive classroom behavior ($P<.05$). No significant differences between AC and ACTC |
| Problem Solving Skills Training[4]<br><br>group were within the SOR: **B** | A 20- to 25-session individual child skills training.<br><br>(PSST) and with PT | 33% (parent report) to 57% (teacher report) of the PSST group and 64%–69% Assessed individually of the PSST+PT<br><br>normal range after treatment. Gains maintained at 1 year. No control group.<br><br>In an inpatient population, PSST showed greater decreases in externalizing and aggressive behaviors than controls ($P<.01$)[5] |
| Dina Dinosaur Social Emotional and Problem Solving Child Training/ Incredible Years Child Training[6]<br><br>SOR: **B** | An 18- to 22-session group skills training program. Assessed as an independent treatment and with PT | PT and PT+CT groups demonstrated fewer mother-reported behavior problems at post-test. Effect sizes: PT vs. control = .89 ($P<.05$); PT + CT vs. control = .73 ($P<.05$)<br><br>One-year follow-up: compared with baseline, 95% of children in the PT+CT group, 74% in the CT group, and 60% in the PT group exhibited at least a 30% reduction in home-observed deviant behaviors. The difference between the PT + CT and PT groups was significant ($P<.01$) |
| Incredible Years Teacher Training[7]<br><br>SOR: **B** | A classroom teacher training program. Assessed with PT, CT and PT+CT | Per parent report, 55% (PT + CT + TT), 59% (PT + TT), 47% (CT + TT) and 20% (control group) had a reduction of 20% or more in behavior problems. The difference between the control group was significant for the PT + CT + TT and PT + TT groups.<br><br>Two-year follow-up: 75% of treated children were within the normal range per parent and teacher reports. No control group. |

AC = Anger coping therapy; ACTC = Anger coping therapy with teacher consultation;
CT = Child Training; PSST = Problem Solving Skills Training;

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An important role for the FP is to convince parents that their participation is critical to treatment

corresponded to a drop in scores of approximately 1 standard deviation.

## RECOMMENDATIONS FROM OTHERS

Two parent training interventions meet the American Psychological Association's criteria for well-established treatments.[9] These include programs based on Patterson and Gullion's Living with Children, a short-term, behavioral parent training program, and programs based on Webster-Stratton's Videotape Modeling parent training program. Two additional treatments, Anger Coping Therapy and Problem Solving Skills Training, meet the criteria for "probably efficacious."

According to the International Consensus Statement on ADHD and Disruptive Behavior Disorders, "pharmacological treatment of pure ODD should not be considered except in cases where aggression is a significant, persistent problem."[10]

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## CLINICAL COMMENTARY

### Psychological interventions for parent and child are essential

Oppositional and defiant behaviors are a family problem requiring a family solution. Frustrated parents often request a "quick fix," so this literature review is helpful in defining when medications are not indicated. Psychological interventions for the parents and for the child are essential. An important role for the family physician is to convince parents that their participation is critical in treating this problem. In addition to encouraging referrals to psychological resources in the community and occasionally prescribing medication, another role for the physician is to model parenting skills. The physician can demonstrate the "Tough Love" philosophy of holding the child responsible for unacceptable behavior without rejecting the child or blaming other people. An additional role could be to schedule brief checkup/counseling sessions with the family and child. These roles can be time consuming without necessarily having the assurance that all of them are evidence-based. However, the value of having multiple role options is that family physicians can develop an individualized approach for helping each family, as long as the

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emphasis remains on parental involvement.

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## What is the most effective treatment for ADHD in children?

### EVIDENCE-BASED ANSWER

Stimulant medication therapy is the most effective treatment for attention deficit/hyperactivity disorder (ADHD) in children, producing significant improvements in symptoms and modest improvements in academic achievement (strength of recommendation [SOR]: **A**, based on multiple randomized controlled trials [RCTs]). Nonpharmacologic therapies, such as behavior therapy, school-based interventions, and family therapy, are not as effective as stimulants but may add modest benefit to the effects of medication (SOR: **B**, based on 1 RCT).

While atomoxetine (Strattera) improves the symptoms of ADHD (SOR: **A**, based on multiple RCTs), stimulant medications other than methylphenidate offer no distinct short-term advantages (SOR: **A**, based on meta-analyses of multiple RCTs). Combination drug therapies offer no significant advantage to stimulants alone unless a comorbid condition is present (SOR: **A**, based on a meta-analysis of 20 RCTs).

The combination of methylphenidate and clonidine (Catapres) improves symptoms in children with both ADHD and tics (SOR: **B**, based on 1 RCT). Clonidine is less effective alone and has significant side effects (SOR: **B**, based on a meta-analysis of nonrandomized trials).

### EVIDENCE SUMMARY

In numerous systematic reviews, RCTs, and meta-analyses, 70% of children responded to stimulant medications with short-term improvements in ADHD symptoms (inattention and hyperactivity/impulsivity) and academic achievement. A forty-year review looked at 135 trials and 413 RCTs of methylphenidate in over 19,000 children with an average age of 8.8 years (range, 8.3–9.4 years) for an average duration of 6 weeks (range, 3.3–8.0 weeks).[1–3]

Study groups included mostly elementary school–aged male children, with few minorities represented. Comorbid conditions, present in 65% of children with ADHD, were often poorly controlled. Outcome measures varied among studies.[3]

The effect size from stimulant medication in these studies averaged 0.8 for symptom relief and between 0.4 and 0.5 for academic achievement. (Effect size is the difference between the means of the experimental and control groups expressed in standard deviations. An effect size of 0.2 is considered small, 0.5 is medium, and 0.8 is considered moderate to large.)

A large randomized trial of 579 children with ADHD (20% girls) aged 7 to 9.9 years compared outcomes of 4 treatment strategies: stimulant medication, intensive behavioral treatment, combined stimulant medication and behavioral interventions, and standard community care.[4] All children met the *DSM-IV* criteria for ADHD Combined Type (the most common type of ADHD in this age group). The stimulant medication strategy included an initial dose titration period followed by monthly 30-minute visits. Intensive behavioral treatment involved child, parent, and school personnel components of therapy. Combination therapy added the regimens for medication and behavioral treatment together. Standard community care consisted of usual (nonsystematic) care, evaluated at 6 different sites.

After 14 months of treatment, children in the medication group and the combined treatment groups showed more improvement in ADHD symptoms than children given intensive behavioral treatment or those who received standard community care. When combined with medication, those treated with behavioral therapy

TABLE

**Commonly used medications for ADHD**

| Medication | Starting dose | Maximum dose | Monthly cost (generic) |
|---|---|---|---|
| Methylphenidate | 5–10 mg 2–3 times daily | 45 mg/d | $20 |
| Dextroamphetamine | 5 mg 1–2 times daily | 40 mg/d | $18 |
| Amphetamine/ Dextroamphetamine | 5 mg 1–2 times daily | 60 mg/d | $50 |
| Atomoxetine | 40 mg once daily | 100 mg/d | $86 |

**Common adverse drug reactions** for all ADHD medications: Nervousness, insomnia, dry mouth, anorexia, abdominal pain, nausea, constipation, palpitations, tachycardia.

showed slight improvement in social skills, anxiety, aggression, oppositional behavior, and academic achievement over medication alone. At the conclusion of the study, 74% of the 212 children on medication were successfully maintained on methylphenidate alone, 10% required dextroamphetamine, and no children required more than one medication. This study found that higher doses of medication with more frequent office follow-up and regular school contact were important features of successful treatment. Only 40% of families were able to complete the intensive behavioral therapy.

Several short-term reviews and meta-analyses show that side effects from stimulant medications are mild and have short duration.[5] More long-term studies are required to evaluate effects on growth. RCTs have limited power to detect rare adverse events that may be better detected by large observational studies.[6]

Atomoxetine, a specific norepinephrine reuptake inhibitor, is an FDA-approved alternative to stimulants for ADHD treatment in children and adolescents. Based on 3 RCTs[7] of 588 children between the ages of 7 and 18 years, atomoxetine showed dose-related improvement in ADHD rating scales. Side effects of atomoxetine are similar to stimulants and include mild but significant increases in blood pressure and pulse.[7]

A meta-analysis of 11 non-randomized trials using clonidine for ADHD showed a smaller effect size compared with stimulants.[8] One RCT of 136 children with ADHD and tics showed improvement of both problems with the use of methylphenidate and clonidine, particularly in combination.[9] Second-line medications such as clonidine, pemoline (Cylert), and tricyclic antidepressants have more potential serious side effects and are not well studied.[10]

## RECOMMENDATIONS FROM OTHERS

The American Academy of Pediatrics recommends that clinicians: 1) manage ADHD as a chronic illness, 2) collaborate with parents, the child, and school personnel to define specific desired outcomes, 3) use stimulant or behavioral therapy to improve these outcomes; if one stimulant is not effective at the highest feasible dose, try another, 4) reevaluate the diagnosis, treatment options, adherence, and possible coexisting conditions if treatment is not achieving the desired outcomes, and 5) follow-up

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**Education and behavioral therapy often improves patient satisfaction and compliance with medication**

regularly with parents, child, and teachers to monitor for progress and adverse effects.[11]

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## CLINICAL COMMENTARY

### When patients, parents, and teachers are educated, we achieve better outcomes

Stimulants and atomoxetine improve symptoms of ADHD quite effectively, making office treatment of ADHD a gratifying experience. Like many other diagnoses, there are numerous medications available to treat ADHD. Becoming familiar with a few and regularly prescribing them makes the treatment of ADHD more comfortable for the physician.

Sometimes patients and parents are hesitant to take medication for ADHD. Education about ADHD, along with trials of behavioral therapy, often improves patient satisfaction and compliance with medication. Likewise, children and adolescents may resist medication because of stigma or feeling unfairly labeled with a disease. Because of this, it is helpful to choose a medication with a long duration, so school dosing can be avoided. Artful negotiation with the patient and parent is beneficial.

In my experience, when patients, parents, and teachers are well-educated about ADHD and use behavioral therapy along with medication, we achieve better outcomes. Useful information for physicians and parents regarding medication use and behavioral therapy are described in the American Academy of Pediatrics ADHD Toolkit available at www.nichq.org/resources/toolkit.

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# What is the interval for monitoring warfarin therapy once therapeutic levels are achieved?

## EVIDENCE-BASED ANSWER

The international normalized ratio (INR) should be measured monthly once therapeutic levels are achieved and are stable for at least 8 weeks, although treatment should be individualized and an increased frequency may be required by some patients (**Table**) (strength of recommendation [SOR]: **C**, consensus statements). For highly compliant patients with stable levels and a clear understanding of factors that influence anticoagulation (changes in health, diet, medications), routine monitoring may be extended to 6 weeks (SOR: **B**, single randomized controlled trial [RCT]) or longer (SOR: **C**, case series). Patient-managed warfarin therapy, using biweekly self-measurements, results in more time in therapeutic range than routine physician-managed care (SOR: **A**, RCTs).

## EVIDENCE SUMMARY

Under- or over-treatment with warfarin can result in life-threatening complications. Limited research exists to guide the selection of an interval for monitoring anticoagulation in stabilized patients. One RCT compared INR monitoring in an anticoagulation clinic at 6 weeks and 4 weeks among 124 patients with a prosthetic heart valve on stable oral anticoagulant treatment and found no difference in thromboembolic or hemorrhagic events.[1] A study in the United Kingdom used a 14-week interval for selected patients, but it used no comparison group.[2] Kent et al developed a computer-based model to compute the optimum interval for monitoring anticoagulation that considers the variability of the patient's previous levels and costs associated with testing and potential complications. This model achieved a maximum interval of 11 weeks for very stable patients.[3]

More frequent testing results in higher time in therapeutic range, particularly when patients self-monitor. A German study of 200 patients with prosthetic heart valves found that they tested within a therapeutic range 48% of the time when monitored by their physician "as usual" (average interval 24 days), and 64% of the time when the interval was increased to 2 weeks.[4] When the same patients then went to self-monitoring every 8, 4, and 2 days, they achieved therapeutic levels 76%, 89%, and 90% of the time, respectively. Bleeding and thromboembolic complications were not reported, but have been demonstrated elsewhere to be lower among patients who self-test frequently (eg, twice weekly) when compared with usual care (average interval 19 days) (4.49% and 0.9% vs 10.9% and 3.6%; number needed to treat [NNT]=15.6 for bleeding, NNT=37 for thromboembolism).[5]

## RECOMMENDATIONS FROM OTHERS

The American College of Chest Physicians (ACCP) recommends individualizing management as the optimal frequency of INR monitoring varies according to patient compliance, dosing decisions, duration of therapy and changes in health, diet, or medications.[6] The ACCP, the American Heart Association,[7] Micromedex DrugPoints System,[8] Goodman and Gilman's *Pharmacological Basis of Therapeutics*,[9] and Cecil's *Textbook of Medicine*[10] all recommend monthly monitoring once stable. The Institute for Clinical Systems Improvement's *Anticoagulation Therapy Supplement Management*[11] and *Managing Oral Anticoagulation Therapy Clinical and Operation al Guidelines*[12] also recommend monthly monitoring for stable patients, but suggest that the interval can be increased to 6 weeks for selected stable patients.

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TABLE

**Approach to monitoring of INR for long-term anticoagulation**

| Clinical scenario | Suggested approach |
|---|---|
| Initiation of warfarin | Monitor daily until stable, then gradually increase interval to weekly, biweekly, monthly if stable |
| INR reaches therapeutic level | Recheck 2 weeks x 2, then every 4 weeks if stable |
| INR therapeutic for 8 to 10 weeks consecutively | May increase interval to 6 weeks with high compliance and good patient education; increase frequency with illness, medication change, history of highly variable INR levels |
| INR outside target range within 1.0 points | Recheck in 1 to 2 weeks; if persists, adjust dose and recheck in 1–2 weeks |
| INR >1.0 points from target range but less than 5 | Adjust dose, recheck in 1 week |
| INR between 5 and 8.9 | Hold warfarin 1 to 2 days, recheck 24 to 48 hours, adjust dose, consider oral vitamin K, but may lead to warfarin resistance |
| INR >9 | Hold warfarin, closely monitor. Bleeding risk increases with higher INR levels. Management may include admission, administration of oral or IV vitamin K, transfusion with fresh frozen plasma if INR very high or high risk of bleeding |

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## ■ CLINICAL COMMENTARY

### Clear and consistent communication between physician and patient is essential

Once a month warfarin monitoring remains a sensible interval after the therapeutic level is achieved. Maintaining a standard routine simplifies the many instructions that physicians give and patients receive. This clear, consistent plan can improve coordination of

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care by medical staff and compliance by patients. Additionally, monitoring has secondary benefits; it reinforces the risks associated with warfarin, and it provides further opportunities to educate the patient.

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## What are the causes of hypomagnesemia?

### EVIDENCE-BASED ANSWER

The causes of magnesium depletion and hypomagnesemia are decreased gastrointestinal (GI) absorption and increased renal loss. Decreased GI absorption is frequently due to diarrhea, malabsorption, and inadequate dietary intake. Common causes of excessive urinary loss are diuresis due to alcohol, glycosuria, and loop diuretics.

Medical conditions putting persons at high risk for hypomagnesemia are alcoholism, congestive heart failure, diabetes, chronic diarrhea, hypokalemia, hypocalcemia, and malnutrition (strength of recommendation: **C**, based on expert opinion, physiology, and case series). Evidence suggests that magnesium deficiency is both more common and more clinically significant than generally appreciated.

### EVIDENCE SUMMARY

**Prevalence and incidence.** In general, studies are limited by variations in analytic techniques and differences in defining the lower limit for normal serum magnesium.[1] Estimates of the prevalence of hypomagnesemia in the general population range from 2.5% to 15%. A study of 11,000 white urban Americans aged 45 to 64 years (probability sampling) found 2.5% with magnesium <0.7 mmol/L and 5% with magnesium <0.75 mmol/L; rates for 4000 African Americans were twice as high.[2]

Some authors have proposed a higher range for normal serum magnesium, asserting that dietary magnesium deficiency is endemic in developed countries where acid rain reduces the magnesium content of crops and food processing causes further large reductions in the magnesium content of the diet.[1] Moreover, common diseases are associated with hypomagnesemia and likely contaminate studies of "normal" populations. Thus, a study of 16,000 German subjects (including blood donors, outpatients, and children) found a 14.5% prevalence of hypomagnesemia using a lower limit of 0.76 mmol/L[1]; however, applying the more commonly cited lower limit of 0.70 mmol/L (1.7 mg/dL) to the same data yielded a prevalence of 2%.

Numerous studies agree that the prevalence of hypomagnesemia is much higher (10%–65%) in subpopulations defined by severity of illness (hospitalization, in intensive care unit [ICU] or pediatric ICU), increasing age (elderly/in nursing home), or specific diseases. For example, of 94 consecutive patients admitted to the ICU, 65% had hypomagnesemia.[3] Likewise, for 127 consecutive patients admitted with a diagnosis of alcoholism, the prevalence was 30%.[4]

Because of limitations noted above, as well as the lack of control groups, the relative prevalence in these groups (compared with the general population) is uncertain, but the studies do identify high-risk populations. A single study, which included a control group, demonstrated an 11% prevalence of hypomagnesemia among 621 randomly selected hospitalized patients compared with 2.5% among 341 hospital employees.[5] Other diseases associated with a high prevalence of hypomagnesemia include cardiovascular disease (hypertension, congestive heart failure, coronary artery disease), diabetes, diarrhea, diuretics use, hypokalemia, hypocalcemia, and malabsorption.[6–9]

**Common causes.** We found no high-quality studies to establish the relative probabilities of various causes in the general population or any subpopulation.[10] The most common causes of significant hypomagnesemia in developed coun-

TABLE

**Causes of hypomagnesemia**

| |
|---|
| **Gastrointestinal** |
| Diarrhea, dietary deficiency (including protein-calorie malnutrition, parenteral and enteral feeding with inadequate magnesium, alcoholism, and pregnancy), familial magnesium malabsorption, gastrointestinal fistulas, inflammatory bowel disease, laxative abuse, malabsorption (sprue, steatorrhea, chronic pancreatitis), nasogastric suction, surgical resection, vomiting |
| **Renal** |
| Alcoholism, diabetes, diuretics (thiazide, loop, and osmotic/hyperglycemia), other medications, hormones (hypoparathyroidism, hyperthyroidism, hyperaldosteronism, SIADH (syndrome of inappropriate antidiuretic hormone secretion), excessive vitamin D, ketoacidosis, renal disease (acute tubular necrosis, interstitial nephritis, glomerulonephritis, post-obstructive diuresis, post-renal transplantation), hypercalcemia/hypophosphatemia, tubular defects (primary magnesium wasting, Welt's syndrome, Gitelman's syndrome, renal tubular acidosis) |
| **Shifts from extracellular to intracellular fluid** |
| Acidosis (correction of), blood transfusions (massive), epinephrine, hungry bone syndrome, insulin/glucose/refeeding syndrome, pancreatitis (acute) |
| **Transdermal losses** |
| Excessive sweating, massive burns |

tries are said to be diabetes, alcoholism, and the use of diuretics. In a group of 5100 consecutive patients (predominantly outpatient, middle-aged, and female) presenting to a diagnostic lab, the most common diagnoses associated with hypomagnesemia were diabetes (20% of cases) and diuretic use (14% of cases); however, other potential causes, including alcoholism, were not identified.[11] A complete list of causes is in the **Table**.

**Serious causes.** A critical serum magnesium level is less than 0.5 mmol/L and is associated with seizures and life-threatening arrhythmias.[6] Very low magnesium levels typically result when an acute problem is superimposed on chronic depletion. For example, critical levels can occur among patients with diabetes during correction of ketoacidosis or alcoholics who develop vomiting, diarrhea, or pancreatitis.

Magnesium in the 0.5 to 0.7 mmol/L range may be life-threatening in certain disease contexts, such as acute myocardial infarction or congestive heart failure, where there is already a risk of fatal arrhythmia.[8]

**Impact.** The impact of hypomagnesemia is underestimated largely because clinicians fail to measure magnesium.[12] Since magnesium is a cofactor for more than 300 enzymes and is involved in numerous transport mechanisms, it is not surprising that hypomagnesemia is associated with significant morbidity.

For example, in a study of 381 consecutive admissions at an inner-city hospital,[13] approximately half the admissions went to ICUs and half to regular wards. Despite similar Acute Physiology and Chronic Health Evaluator (APACHE) scores at admission, hospital mortality was twice as high for hypomagnesemic patients in both care settings.

## RECOMMENDATIONS FROM OTHERS

Several review articles include a comprehensive differential diagnosis for causes of

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magnesium deficiency based on physiologic principles as listed in the Table, but none provide data on the relative frequency of the various causes in the general population or specific subgroups.[6–9]

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## CLINICAL COMMENTARY

### We need to know when magnesium replacement improves patient outcomes

Treating the underlying cause of hypomagnesemia makes sense. However, even though clinicians often treat "the numbers," it is not clear that magnesium replacement therapy is beneficial in the absence of symptoms caused by the hypomagnesemia. For example, hypomagnesemia is common for patients with acute myocardial infarction, but magnesium replacement therapy has not been shown to improve outcomes in 2 large randomized trials, the Fourth International Study of Infarct Survival (ISIS 4)[14] and Magnesium in Coronaries (MAGIC).[15] We need better-designed randomized trials to know for what clinical conditions magnesium replacement leads to improved patient-oriented outcomes.

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# What are effective therapies for *Clostridium difficile*–associated diarrhea?

## EVIDENCE-BASED ANSWER

Oral metronidazole and oral vancomycin are equally effective treatments for *Clostridium difficile*–associated diarrhea (CDAD) (strength of recommendation [SOR]: **A**, based on randomized trials). Oral vancomycin is considerably more expensive and may select for colonization with vancomycin-resistant enterococci, leading the American College of Gastroenterology to recommend oral metronidazole as preferred therapy (SOR: **C**, expert opinion). They recommend therapy with vancomycin for those who are pregnant, breast feeding, less than 10

TABLE

**Medical treatment of *C difficile*–associated diarrhea**

| Indication | Treatment |
|---|---|
| First episode of *C difficile*–associated diarrhea (SOR: **A**; SOR: **C** for preference over vancomycin) | Metronidazole, 500 mg orally 3 times daily for 10 days |
| First episode, allergy, or intolerance to metronidazole, pregnant, breast feeding, or age <10 years (SOR: **A**; SOR: **C** for preference over metronidazole) | Vancomycin, 125 mg orally 4 times daily for 10 days |
| Unable to take oral medication (SOR: **C**) | Metronidazole 500 mg IV 4 times daily |
| First recurrence (SOR: **C**) | As for first episode or Option #1 below |
| Second or greater recurrence:<br>Option #1 (SOR: **B**, single RCT) | Metronidazole or vancomycin, plus *S boulardii* (500 mg twice daily [3 x $10^{10}$ CFUs]) |
| Option #2 (SOR: **C**) | Vancomycin or metronidazole<br>plus rifampin 300 mg<br>oral twice daily for 10 days |
| Option #3 (SOR: **C**) | Vancomycin tapered dose:<br>125 mg orally 4 times daily for 7 days<br>125 mg orally twice daily for 7 days<br>125 mg orally once daily for 7 days<br>125 mg orally every other day for 7 days<br>125 mg orally every 3 days for 14 days |
| Option #4 (SOR: **C**) | Vancomycin plus cholestyramine<br>4 g twice daily for 10 days |

years old, nonresponders to metronidazole, critically ill, or allergic or intolerant to metronidazole (SOR: **C**, expert opinion).

Treat first recurrences the same as primary infection. In persons with recurrent infection, addition of the probiotic agent *Saccharomyces boulardii* reduces the risk of further recurrences (SOR: **B**, single RCT). Little other evidence exists to guide therapy for subsequent recurrences.

## EVIDENCE SUMMARY

Two randomized controlled trials have compared the efficacy of oral metronidazole and oral vancomycin for treatment of CDAD.[1,2] Both studies demonstrated statistically equivalent cure rates exceeding 90%, with relapse rates of 10% to 20% for each drug. These small trials lacked the power to detect small but potentially significant differences in treatment response.

No published data exist indicating that vancomycin is more effective than metronidazole in any clinical setting. A dose-range study showed that 125 mg of oral vancomycin 4 times a day is as effective as higher doses.[3] Patients who cannot take medication by mouth should receive intravenous metronidazole, 500 mg 4 times per day. Unlike vancomycin, metronidazole achieves potentially effective concentrations in the intestinal lumen following intravenous administration.[4]

Treatment of first recurrences of infection with metronidazole or vancomycin produces response rates similar to treatment of initial

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For those with recurrent infection, addition of *S boulardii* decreased the absolute risk of relapse by 30%

infections.[5] A minority of patients suffers multiple relapses of infection, and there are few data to guide therapy in this setting.

A randomized, double-blinded, placebo-controlled study evaluated the impact of adding the probiotic agent *Saccharomyces boulardii* to either metronidazole or vancomycin.[6] For persons with recurrent infection, addition of *S boulardii* led to a 30% decrease in the absolute risk of relapse (64% relapse vs 34%; number needed to treat=3; $P<.05$). There was also a nonsignificant trend toward reduced recurrences in the treatment of primary infections. The 2 minor side effects noted with this treatment were dry mouth (number needed to harm [NNH]=11) and constipation (NNH=9). *S boulardii* capsules are available from health food stores and via the Internet. Several published case series describe various additional approaches to therapy of recurrent CDAD (**Table**).

## RECOMMENDATIONS FROM OTHERS

The American College of Gastroenterology and the American College of Physicians treatment guidelines for CDAD both call for treatment with oral metronidazole 250 mg 4 times daily or 500 mg 3 times daily.[7,8] The American College of Gastroenterology recommends vancomycin (125 mg orally 4 times daily) when there is an intolerance or confirmed resistance to metronidazole, failure of response, when the patient is pregnant, breast feeding, or under 10 years of age, critically ill from colitis, or when the diarrhea could be related to *Staphylococcus aureus*. In milder cases, treatment may involve only discontinuation of antibiotics and supportive therapy with observation. Opiates and antispasmodics should be avoided. These guidelines do not recommend any treatment over another for therapy of multiple recurrences.

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## CLINICAL COMMENTARY

### Discontinue the offending antibiotic and treat the infection; prevent outbreaks via patient-to-patient transmission

Most cases of *Clostridium difficile*–associated diarrhea are caused by antibiotic use; it is therefore one of the most common nosocomial infections. In addition to discontinuing use of the offending antibiotic and treating the infection, it is also important to prevent further outbreaks via patient-to-patient transmission. In our hospital, once a patient is diagnosed with *C difficile*, contact precautions are instituted. If the patient is incontinent, isolation in a single room is required. If the patient is continent