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*Putting Evidence into Practice*

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## Magnesium Sulfate for Prevention of Preterm Birth

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### Clinical Question

Is magnesium sulfate a safe and effective treatment for preterm labor?

### Evidence-Based Answer

Magnesium sulfate does not delay delivery when used in patients with preterm labor. Although magnesium sulfate is not associated with any serious adverse maternal outcomes, it may be associated with an increase in total fetal, neonatal, and infant mortality. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

### Practice Pointers

Preterm birth, defined as occurring before 37 weeks of gestation, is the leading cause of neonatal death and is associated with several short- and long-term infant morbidities. Tocolytics, agents that inhibit uterine contractions, are commonly used to prevent or delay preterm birth. Magnesium sulfate is one of the most commonly used tocolytics in the United States.[1] An earlier pooled analysis of five trials involving 6,145 infants with similar inclusion criteria found a statistically significant benefit of magnesium sulfate as a neuroprotective agent (relative risk [RR] = 0.68; 95% confidence interval [CI], 0.54 to 0.87; number needed to treat = 63).[2]

This review included 37 studies, with a total of 3,571 women, in which magnesium sulfate was compared with no treatment, placebo, or one of several alternative tocolytic agents. Studies varied with respect to the gestational ages included (less than 30 weeks to up to 37 weeks), loading dosage of magnesium sulfate (4 to 8 g per hour), and maintenance dosage (1 to 6 g per hour). Primary outcomes included birth within 48 hours of trial entry, serious maternal outcomes, and serious infant outcomes, including death. Secondary outcomes included maternal adverse drug reactions and infant admission to the neonatal intensive care unit.

Delivery within 48 hours of magnesium sulfate administration was reported in 19 trials that included 1,913 women. There were no significant differences in the risk of birth within 48 hours between women who received magnesium sulfate and those who received no medication, placebo, or any other tocolytic agent. The exact RR varied depending on the comparison agent, but none were statistically significant.

Serious infant outcomes, defined as death, chronic lung disease, grade III-IV intraventricular hemorrhage or periventricular leukomalacia, or major neurosensory disability, were reported in 18 trials. None of these reached statistical significance. Magnesium sulfate administration also did not have significant effects on any less serious neonatal morbidities studied, including five-minute Apgar score of less than 7, respiratory distress syndrome, need for assisted ventilation, or necrotizing enterocolitis.

When analyzed individually, the risks of death for fetuses, neonates, and infants were not significantly increased in those whose mothers were given magnesium sulfate vs. placebo. In the same regard, magnesium sulfate did not increase the risk of death for fetuses, neonates, and infants when compared with other tocolytic agents.[3] However, when analyzed as an aggregate, the risk was increased (RR = 4.56; 95% CI, 1.00 to 20.86). It should be noted that these data are driven by the outcomes of one study of 167 patients, in which all the deaths occurred. Seven trials that included 930 women evaluated serious maternal outcomes, defined as death, cardiac arrest, respiratory arrest, or admission to an intensive care unit. None of these outcomes were reported in any of the seven trials.

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Recent concern about safety has led the U.S. Food and Drug Administration to advise against the use of magnesium sulfate for more than five to seven days. This recommendation was specifically related to concerns about neonatal hypocalcemia and osteopenia.[4] The American College of Obstetricians and Gynecologists has recommended that use of magnesium sulfate as a tocolytic be limited to 48 hours in women from 24 to 34 weeks' estimated gestational age.[5]

The current literature on magnesium sulfate in preterm labor presents a mixed picture of risks and benefits. However, it is clear that magnesium sulfate should not be used as a tocolytic agent. Family physicians should be aware that magnesium sulfate may be considered as a neuroprotective agent for neonates whose mothers have preterm labor after careful consideration of risks and benefits. However, more research is needed to identify which patients are likely to benefit from the addition of magnesium sulfate in the setting of preterm labor.

SOURCE: Crowther CA, Brown J, McKinlay CJ, Middleton P. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev.* 2014;(8):CD001060.

The practice recommendations in this activity are available at http://summaries.cochrane.org/CD001060.

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## Immediate-Release Methylphenidate for the Treatment of ADHD in Adults

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### Clinical Question

Should we prescribe immediate-release methylphenidate (Ritalin) to adults with attention-deficit/hyperactivity disorder (ADHD)?

### Evidence-Based Answer

In adults with ADHD, immediate-release methylphenidate improves symptoms of hyperactivity, impulsiveness, and inattentiveness compared with placebo. Short-term adverse effects such as weight loss and decreased appetite do not appear to be serious. However, larger studies of longer duration are needed to evaluate for cardiovascular outcomes. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

### Practice Pointers

ADHD is a common diagnosis in primary care, with an estimated prevalence of 4.4% in the adult population.[1] An estimated 35% of children with ADHD still meet criteria for ADHD as adults.[2] Many more children will no longer meet criteria for ADHD as adults, but will continue to manifest some of the core symptoms (i.e., hyperactivity, inattentiveness, or impulsiveness). Compared with control patients, adults with ADHD are more likely to have other psychiatric comorbidities (e.g., anxiety, bipolar disorder, substance abuse), interpersonal impairments, and difficulty with employment.[2]

This Cochrane review included 11 randomized, double-blind, placebo-controlled trials examining the effectiveness of immediate-release methylphenidate in 474 participants. Compared with placebo, methylphenidate decreased symptoms of hyperactivity with a standardized mean difference (SMD) of –0.60 (95% confidence interval [CI], –1.11 to –0.09); inattentiveness with an SMD of –0.66 (95% CI, –1.02 to –0.30); and impulsiveness with an SMD of –0.62 (95% CI, –1.08 to –0.17). Looking at the overall change in condition, the pooled studies demonstrated an SMD of –0.72 (95% CI, –1.12 to –0.32), favoring methylphenidate over placebo.

The effects of treatment with methylphenidate on anxiety and depression symptoms were equivocal; some studies showed benefit, whereas others demonstrated no effect. Subgroup analysis showed high-dose methylphenidate (more than 0.9 mg per kg per day) to be no more effective than low-dose methylphenidate (0.9 mg per kg per day or less) in treating hyperactivity, impulsiveness, or inattentiveness.

The main adverse effects of methylphenidate use in children also pertain to adults. Decreased appetite was reported in six studies, and significant weight loss was reported in three studies. Insomnia, jitteriness, sweating, and tremor also occurred. There were reports of significantly elevated blood pressure and heart rate in some of the studies, but none revealed an increased risk of cardiovascular events or death. The number of patients studied is too small and the length of the trials is too short to detect a clinically important increase in cardiovascular events, if one exists.

This Cochrane review concluded that, compared with placebo, immediate-release methylphenidate is an effective treatment for adults with ADHD, but the review had some limitations. The study participants were limited to individuals from the United States, Canada, and the Netherlands without significant comorbid psychiatric issues, so caution must be used when generalizing the results to other populations. Because the trials span approximately 35 years, there is some variation in the assessment tools used and the diagnosis rates. The size (the largest included 146 participants) and duration (the longest was 17 weeks) of the trials impose serious limitations for detecting long-term adverse effects and the effectiveness of methylphenidate over time. Despite these limitations, the included trials provide evidence in support of current recommendations that methylphenidate be considered first-line therapy in the management of adult ADHD.[3]

SOURCE: Epstein T, Patsopoulos NA, Weiser M. Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. *Cochrane Database Syst Rev.* 2014;(9):CD005041.

The practice recommendations in this activity are available at http://summaries.cochrane.org/CD005041.

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