

# How (not) to dose antidepressants and antipsychotics for children

## Knowing pharmacokinetics can improve efficacy, help avoid adverse effects

**W**here do you turn for help in dosing an antidepressant for a child with major depressive disorder? You might be misinformed if you rely on methods used in multicenter, randomized, placebo-controlled trials, according to Robert L. Findling, MD, an expert in child and adolescent pharmacokinetics (PK).

In a recent review,<sup>1</sup> Dr. Findling and colleagues at University Hospitals, Case Medical Center, and Case Western Reserve University concluded that:

- Data from PK studies do not support the dosing strategies used in many placebo-controlled efficacy trials of antidepressants in children and adolescents
- Excessively low or high dosages may explain—at least in part—why antidepressants failed to show efficacy or were associated with agitation, hostility, or increased suicidality among depressed pediatric patients in some studies.

To provide CURRENT PSYCHIATRY readers with more information on this topic, Section Editor Robert A. Kowatch, MD, PhD, interviewed Dr. Findling about pediatric PK studies and what they can tell clinicians about dosing antidepressants and antipsychotics in children and adolescents.

### Not ‘small adults’

**Dr. Kowatch:** Warnings about a risk of suicidality in young people taking antidepres-



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sants have increased physicians' concern about accurate dosing for children. How do pediatric pharmacokinetic parameters differ from those of adults?

**Dr. Findling:** Children and adolescents are not, of course, simply small adults. Significant differences in absorption rate, volume of distribution, and elimination affect PK parameters, such as half-life, throughout the life cycle.<sup>2</sup>

**Dr. Kowatch:** What determines these differences? Are they based on factors such as weight, age, puberty, or gender?

**Dr. Findling:** In general, PK differences observed with antidepressants have been dependent on the patient's age or weight, rather than on gender differences or sexual maturation. To assume that drug exposure

### Clinical Point

Excessive doses may explain in part why antidepressants caused agitation, hostility, and suicidality in some trials with depressed pediatric patients

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'Paroxetine has nonlinear kinetics; doubling the dose from 10 to 20 mg/d results in a 7-fold increase in serum concentration in kids'

is weight-proportional across the life cycle is fraught with peril and is not true for many compounds, including psychotropics.

**Dr. Kowatch:** In which age groups would clinicians see the greatest differences in drug exposure?

**Dr. Findling:** It depends on the compound. Exposure to lithium, for example, is determined by the glomerular filtration rate, which often is much higher and necessitates higher weight-adjusted dosing in a younger child than in a teenager or adult. Drug exposure becomes more complicated with more complex compounds, with differing volumes of distribution, absorption rates, and perhaps multiple enzymes involved in bio-disposition.

### Factors that affect dosing

**Dr. Kowatch:** Clinically, what's the best way to determine safe, effective psychotropic dosing in children?

**Dr. Findling:** The short answer is to study the literature, and unfortunately most people find PK studies just about as interesting as watching paint dry. But a good PK study provides insight into a very important parameter, which is dosing.

Ultimately, we can't talk about a medicine's effectiveness or safety as a fixed statement. You can't say drug "x" is effective for this condition or drug "y" is associated with this rate of side effects because tolerability and effectiveness are dose-dependent. And if you don't know how to dose a medicine, you can't characterize its pharmacodynamic properties when prescribing it to a youngster.

So you have to know the literature; what happens at different doses is terribly important.

**Dr. Kowatch:** In children with psychiatric disorders, what does the literature say about whether the diagnosis determines the dose?

**Dr. Findling:** With children, dosing may be diagnosis-dependent for the same medications within the same age groups. For example, Tourette's syndrome or conduct disorder in children and adolescents

can be managed with lower antipsychotic doses than those required for major psychotic illnesses or mania. Unfortunately, we see youngsters with major psychotic illnesses or mania who have been prescribed the lower antipsychotic doses used to treat conduct disorder, and we see youngsters with conduct disorder who have been given 2 or 3 times the recommended antipsychotic dosages for that condition.

As you increase the dose you get higher exposure, and with higher exposure you have more side effects. Across the 3 antipsychotics we've studied—risperidone, quetiapine, and aripiprazole—youngsters with conduct disorder need about half or less of the medication needed by those with psychotic illness or mania.

**Dr. Kowatch:** What about dosing selective serotonin reuptake inhibitor (SSRI) antidepressants?

**Dr. Findling:** For some SSRIs, daily weight-adjusted doses are similar across the life cycle. However, there are exceptions. With paroxetine, for example, you get greater drug exposure in young people than in adults, even if you control for weight differences. And paroxetine has nonlinear kinetics in adults and in young patients; when you double the dose, you more than double the exposure.

### Exposure and half-life

**Dr. Kowatch:** Can you talk more about nonlinear kinetics?

**Dr. Findling:** People assume that doubling a dose doubles the patient's exposure to the drug, but that's not necessarily so. In young people, for instance, when the dose of paroxetine is doubled from 10 to 20 mg/d, a 7-fold increase in the drug's serum concentration has been seen<sup>3</sup> (*Table 1*).

In another example, the half-life of citalopram or escitalopram in adults is about 24 hours. In a small pilot study with adolescents, the half-life seemed to be about 19 hours.<sup>4</sup> So what's the half-life in younger children? We simply don't know. If it's even shorter than in teenagers, then maybe we

Table 1

## SSRIs in children and adolescents: What PK studies found

Antidepressant	Findings	Dosing recommendations
Fluoxetine	With chronic 20-mg dosing, blood levels were ~2 times higher in children (ages 6 to 12) than adolescents (ages 13 to 18)	Perhaps start with 10 mg/d for prepubertal children and 20 mg/d for adolescents
Sertraline	With <200 mg/d dosing, shorter half life was seen in youths when compared with adults	Twice-daily dosing might be reasonable for youths receiving <200 mg/d
Paroxetine	Increasing dosage from 10 mg to 20 mg increased blood level 7-fold in youths (nonlinear PK); dosages used in most clinical trials exceeded those supported by PK studies	Consider starting with 10 mg/d; if no response, increasing to 20 mg/d may be reasonable
Citalopram	With chronic 20-mg dosing, S-citalopram half-life (19.2 hours) was shorter in adolescents than reported in adults; no PK data available for children	Twice-daily dosing might be reasonable for adolescents or children
Escitalopram	Half-life of a single 10-mg dose was shorter in adolescents than adults; exposure ~15% greater in adults than adolescents; no PK data available for children	Twice-daily dosing for adolescents or children might be a rational consideration

PK: pharmacokinetic  
SSRIs: selective serotonin reuptake inhibitors

Source: Reference 1

### Clinical Point

'Because sertraline at lower dosages has a shorter half life in kids than adults, twice-daily dosing might be reasonable for youths receiving <200 mg/d'

should be dosing these drugs twice daily in children rather than once daily as we do with adults.

**Dr. Kowatch:** So clinicians need to consider at least 2 different factors: shorter half-lives with most SSRIs in children and the possibility of nonlinear kinetics.

**Dr. Findling:** Yes, and there is greater between-subject variability in PK parameters in children than in adults, based on age and size differences. With sertraline, for example, if you give young people 200 mg/d, the PK parameters are very similar to those of adults. With lower doses, however, sertraline appears to have a shorter half-life that is dose-related. This suggests that if you use dosages <200 mg/d, then maybe sertraline should be given twice daily to depressed youths.

### Different doses, different results?

**Dr. Kowatch:** Your study found that some SSRI dosages used in placebo-controlled trials of children with major depression

were not supported by data from PK studies. Do you think different dosing would have changed the outcomes?

**Dr. Findling:** That's an empiric question, but I think the odds for different results are high. For example, I just alluded to dosing <200 mg of sertraline twice daily, but that was not done in the pivotal efficacy studies. If it had been, would there have been a greater salutary effect and reduced incidence of side effects? The answer is maybe.

**Dr. Kowatch:** What about the increased risk of suicidality in children and adolescents that was seen in clinical trials with paroxetine and venlafaxine (*Table 2, page 82*)? If those antidepressants had been dosed differently, would that adverse effect have disappeared?

**Dr. Findling:** It might not have been as strong. Again, it's an empiric question.

**Dr. Kowatch:** So how does dosing affect the risk of suicidality?

**Dr. Findling:** Among SSRIs, paroxetine was reported in clinical trials to have the

### Clinical Point

'Weight gain with SGAs is worse in kids than in adults, but I have yet to see compelling evidence that suggests why'

Table 2

## Non-SSRI antidepressants in children and adolescents: What PK studies found

Antidepressant	Findings	Comment
Venlafaxine	One PK study exists (6 children, 6 adolescents); systemic exposure was lower than reported in adults when given at ~2 mg/kg/d	Not found more efficacious than placebo in 2 studies of youth ages 7 to 17 with MDD; little evidence exists to support dosages used in these studies, which found the highest risk of suicidality with venlafaxine, compared with other antidepressants
Nefazodone	In open-label, flexible-dose trial, depressive symptoms improved substantially with mean dosages of 233 mg/d in children and 342 mg/d in adolescents	Children may do better using lower dosages than are optimal for adolescents
Mirtazapine	In a single-dose trial of youths age 7 to 17, half-life increased significantly with increasing weight (range 17.8 to 48.4 hours), and blood levels decreased with increasing age	8 weeks of dosing at 15 to 45 mg/d were not superior to placebo in 2 studies of youth ages 7 to 17 with MDD

MDD: major depressive disorder

PK: pharmacokinetic

SSRI: selective serotonin reuptake inhibitor

Source: References 1,5

highest risk of suicidality. Is that because it has nonlinear kinetics and was dosed much higher than was optimal?

PK data suggest an appropriate starting dose of 10 mg/d, with an increase to 20 mg/d after a month, if needed.<sup>5</sup> In the pivotal randomized, controlled efficacy trial, however, the starting dose and escalation rate were much higher. Based on the PK data, a lower starting dose with a more gradual titration strategy might have been used.

**Dr. Kowatch:** So better dosing studies are needed?

**Dr. Findling:** Yes. Clinicians are limited by the lack of methodologically rigorous dosing studies that ascertain PK parameters in children.

### Antipsychotics and weight gain

**Dr. Kowatch:** What about dosing second-generation antipsychotics (SGAs)? Clinicians tend to treat children with lower doses than are used for adults.

**Dr. Findling:** Right, although that practice is not entirely evidenced-based. We learned from an early pilot PK study of aripiprazole<sup>6</sup>

that initially giving adult doses to kids produced emesis and sedation. This suggested that kids respond to this drug differently than adults, and lower starting doses and gradual upward titration were needed to make the drug more safe and effective in kids. That's a perfect example of a dose-ranging study with PK parameter estimates that provide the requisite data to design pivotal studies.

**Dr. Kowatch:** How do pharmacokinetics affect weight gain in children treated with SGAs?

**Dr. Findling:** Weight gain with SGAs is worse in kids than in adults, but I have yet to see compelling evidence that suggests why. In order of weight-gain effect, I would say clozapine and olanzapine are similar, although clozapine probably has the greatest effect. Next would be risperidone and quetiapine having equal effects, followed by aripiprazole and ziprasidone. Aripiprazole seems to cause modest but not terribly problematic weight gain, and ziprasidone seems weight neutral.

But there is some PK variability from patient to patient. In a recent pilot study

of quetiapine,<sup>7</sup> we found that most kids gained weight early and leveled out at a certain threshold, even though dosing remained the same. Only one youngster had problematic weight gain, and we suspect this was because he had higher exposure because of intersubject PK variability.

**Dr. Kowatch:** In children, how do you manage weight gain associated with SGAs and other psychotropics?

**Dr. Findling:** Our group is pretty conservative. We usually don't prescribe weight-loss medications to kids. We also don't send everyone to a dietitian; that's not financially feasible for many families. And studies with risperidone suggest that psychostimulants don't ameliorate weight gain.<sup>8</sup>

That leaves us with preparing pediatric patients for increased appetite when they start SGAs. We talk about healthy snacks—such as unbuttered popcorn instead of potato chips—and advise against drinking soda and juice, which are loaded with calories. We also try to get sedentary kids up and moving. Some kids enjoy video games where they can dance on mats based on prompts on the screen. We also can switch SGAs if a patient is gaining weight; we've got lots of options.

## Dosing is 'not haphazard'

**Dr. Kowatch:** Any final thoughts?

**Dr. Findling:** Dosing is not a haphazard event. It needs to be rigorously and scientifically determined and characterized with well-described studies that often involve ascertaining PK parameter estimates. Can you imagine if somebody gave a new medicine to 10 adults, found some degree of benefit, and then started large-scale, phase-3 studies? No one would think that was reasonable, yet that's what happens with kids all the time.

## Related Resources

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### Drug Brand Names

Aripiprazole • Abilify	Olanzapine • Zyprexa
Citalopram • Celexa	Paroxetine • Paxil
Clozapine • Clozaril	Quetiapine • Seroquel
Escitalopram • Lexapro	Risperidone • Risperdal
Fluoxetine • Prozac	Sertraline • Zoloft
Mirtazapine • Remeron	Venlafaxine • Effexor
Nefazodone • Serzone	Ziprasidone • Geodon

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## Clinical Point

'To manage weight gain associated with SGAs, we prepare pediatric patients for increased appetite and try to get sedentary kids up and moving'